INORGANIC CHEMISTRY

IN PHARMACY

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Preface

There is general agreement, among those charged with the academic training and education of the pharmacist, on the necessity within the curriculum of a course which deals with inorganic chemistry in pharmacy. Such a course is described in the catalogs of various schools as inorganic pharmacy, inorganic pharmaceutical chemistry, the pharmacy of inorganic chemicals, or by a similar descriptive title. The most recent justification of the necessity, and place within the curriculum, of this course is furnished by the Consultive Committee on Physical Sciences and Mathematics in the Pharmacy Curriculum of The Pharmaceutical Survey and by the current Committee on Curriculum of the American Association of Colleges of Pharmacy. These committees recommend a course designed to supplement and augment the descriptive and, by its very nature, general information of the course in beginning chemistry to develop a more adequate basis for the proper handling of inorganic medicinal chemicals by the pharmacist.

Inorganic Chemistry in Pharmacy has been written as a textbook for such type of information. It is intended for a course which follows, and presupposes a knowledge of, general chemistry and qualitative analysis, and may be described briefly as a review of certain principles of inorganic chemistry with special reference to the preparation, properties, testing and uses of inorganic chemicals employed in pharmacy and medicine. Hence it is not intended to serve the purpose of a text on general chemistry and it is, by this very fact, delimited to inorganic substances of pharmaceutical and medicinal interest.

The elements and their compounds are taken up according to the groups in which the elements occur in the periodic table. The compounds are classified and presented, in general, as hydrides of the elements, metallic compounds of the elements or metallic substitution products of the hydrides, hydroxides (oxyacids and bases) of the elements, and salts of the oxyacids or metallic substitution products of the hydroxides. The field of inorganic chemistry has been greatly simplified for this purpose by regarding the majority of the compounds as substitution products of the hydrides and hydroxides of the elements, thus paralleling to some extent the classification of organic compounds. Under each of these subdivisions there is presented the pertinent historical background, natural occurrence, methods of formation and preparation, physical and chemical properties, and uses.

An attempt has been made throughout to avoid the presentation of the subject matter as isolated and unrelated facts but to refer them, wherever possible, to the general principles and properties of which those facts are an expression. As a result, it is hoped that the book will qualify as a textbook rather than a handbook of information. Under methods of formation and preparation, for example, the pharmacist is concerned not only with those methods and reactions by which a chemical is manufactured for commerce but also with those reactions in which the chemical is formed or appears as a result of instability, a test for identity, a test for purity, or an assay process; hence, all of these are given equal emphasis as illustrations. Instead of giving separate attention to such points as stability, storage requirements, tests for identity and purity, incompatibilities, etc., for each

inorganic substance by monographic treatment, as in the U. S. Pharmacopœia and National Formulary, these points have been integrated into and correlated with methods of formation and preparation or physical and chemical properties wherever possible.

In many respects the book may be regarded as a commentary on and as complementary to the U. S. Pharmacopœia and National Formulary and it is intended to serve as a teaching aid, to be used in close conjunction with those standard works. For this reason the repetition of the content and the quotation of passages from those books have been avoided throughout. However, in order to familiarize the student with, and to aid him in an understanding of, much of the wealth of information contained in the U.S.P. and N.F., liberal use has been made of this information for illustration. To facilitate the location of such information, references to specific page numbers in the U.S.P. and N.F. have been included in each instance. Considerations of time and expense in printing and revising have caused these references to be grouped at the end of each chapter.

Former students of the late Professor Edward Kremers will recognize in the book a development and an extension of the manner of approach and method of presentation of inorganic pharmaceutical chemistry which he propounded at the University of Wisconsin for many years. To him the term pharmaceutical chemistry meant simply chemistry which is taught to pharmacy students; his greater concern was that chemistry, not chemicals, be taught in such courses. The book had its beginnings in the first drafts of the manuscripts for a few of the chapters, written by the senior author in 1940-41 in collaboration with Dr. Kremers. The advent of World War II postponed work on the text until recent months when it was resumed by collaboration among the three co-authors. We have endeavored to avoid the danger, inherent in such collaboration, of a book becoming a collection of disjointed, overlapping chapters, and believe that we have been successful in coordinating all of the subject matter into a homogeneous treatise.

For the purpose of record, Chapters 1, 2, 9, 12, 13 and 14 were written by Paul J. Jannke; Chapters 3, 5, 6, 10 and 11 by Lloyd M. Parks; and Chapters 4, 7, 8, 15, 16 and 17 by Loyd E. Harris. We are indebted to Dr. John E. Christian, Associate Professor of Pharmaceutical Chemistry and Co-ordinator of Bio-Nucleonic Research, Purdue University, for Chapter 18 on the Isotopes of the Elements and Their Uses in Pharmacy, Pharmaceutical Research and Medicine.

To those who may see fit to make use of the book the authors will be grateful for suggestions and criticism. The kindness of readers in calling attention to errors will be greatly appreciated.

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Pharmaceutical chemistry is a field of study in which consideration is given to both the pharmaceutical and the chemical aspects of medicinal substances. The chemical aspects of therapeutic agents are physical and chemical properties and methods of preparation and purification, thus accounting for the various tests which are a part of the monographs for many chemicals in the Pharmacopœia and the National Formulary. The pharmaceutical aspects should be concerned primarily with interpretations of physical and chemical properties which are significant in professional practice and with the use of chemicals in pharmaceutical processes, along with incompatibilities and poisons and antidotes.

FACTORS CONCERNING DRUG ACTION

The study of the pharmacodynamics of chemical compounds is relegated to the pharmacologist, who is capable of demonstrating the physiologic action of the compounds on both cells and tissues. However, the pharmacologist alone cannot account fully for the mechanisms of the reactions which are involved. It is generally agreed that the action of a drug depends in part upon the kinds, the numbers and the orientation of the atoms which make up the compound. A partial understanding of the physical chemistry of the cells has enabled pharmacologists to formulate numerous hypotheses and to draw various conclusions, substantiated by experimental evidence, concerning the action of drugs on cells. Drug action involves a chain of reactions generally too complicated to consider here; nevertheless, certain of the basic principles already known to the student can be interpreted to advantage.

Hoebner (1902) and Bechold (1911) were among the first to give a systematic account of the physicochemical properties of cells, while Arrhenius (1915) was one of the first to attempt a general interpretation of drug action by means of the laws of physical chemistry.[1] Because physiologic response results from the interaction of chemicals, the law of mass action is indispensable. Resulting equilibria, as well as the whole living process itself, conform to the laws of Le Châtelier and van't Hoff and the law of partition.

The mode of action of many inorganic chemicals is based upon Arrhenius' theory of electrolytic dissociation. Thus, the sedative action of sodium bromide depends upon the reaction:

$$NaBr \rightleftharpoons Na^+ + Br^-$$

Strontium bromide likewise is a sedative, but its activity is of a different order. The compound is not caustic because of the lack of causticity in the strontium ion, and due to the differences in solubility and the rates and degrees of ionization, the onset of sedation and the duration of it varies between the two bromides. Similarly, the mode of action of sodium nitrite is generally char-

acteristic of the nitrites (ethyl and amyl) and therefore is attributable to the nitrite radical. Again, the onset and the duration of vasodilation are functions of the identity and the properties of the compound, while the basic therapeutic action is a function of the negative ion.

Activity also may be attributable to the positive ion, in which instance the negative ion plays a minor role. In the treatment of hypo-acidity, any ionizable acid can be used because:

$$HCl \rightleftharpoons H^+ + Cl^-$$

and

$$H_2SO_4 \rightleftharpoons 2H^+ + SO_4^{--}$$

Astringent and styptic properties are characteristic of all soluble aluminum salts which ionize strongly.

$$AlCl_3 \rightleftharpoons Al^{+++} + 3Cl^-$$

and

$$Al_2(SO_4)_3 \rightleftharpoons 2Al^{+++} + 3(SO_4)^{--}$$

The effect of ionization is illustrated strikingly by some of the mercury salts. Mercuric chloride ionizes in aqueous solution and is extremely poisonous, while mercuric cyanide, which also is soluble in water, is almost nonionizable and is far less poisonous.[2] The characteristic violently poisonous nature of the cyanide radical is demonstrated by potassium cyanide which is strongly ionized,

$$KCN \rightleftharpoons K^+ + CN^-$$

Potassium ferrocyanide is nonpoisonous because it yields no cyanide ions; this is shown in the equation:[3]

$$K_4Fe(CN)_6 \rightleftharpoons 4K^+ + Fe(CN)_6^{----}$$

When sodium chloride is added to a solution of mercuric chloride, the disinfecting value of the latter decreases due to the common ion effect in which the increased concentration of the chloride ion suppresses the ionization of mercuric chloride.[4] Fewer mercuric ions are formed in accordance with the equation

$$\frac{[Hg^{++}] \times [Cl^-]^2}{[HgCl]} = K_{HgCl_2}$$

The poisoning of enzyme systems by silver depends upon silver combining with the proteins and forming ionizable salts whose ionization constants can be expressed as:

$$\frac{[Ag^+] \times [E^-]}{[AgE]} = K_{AgE} = 10^{-7.4}$$

Poisoning results from the precipitation of the proteins in the enzyme system.[5]

Granting that the rates and the degrees of solution and dissociation are factors which influence the rate of diffusion throughout the body fluids, there are yet to be considered a number of other physicochemical factors. The protoplasm of a cell is inclosed by a membrane which is a mosaic of lipids and proteins. The membrane possesses both an electrical potential (membrane potential) and a definite pH value. Because of these two factors, membrane surface reactions can and do occur, especially in the case of those chemical agents which are active at high dilutions. Membrane potential accounts for the theory of receptor groups, proposed by Ehrlich. These groups provide an attraction for certain kinds of ions which, when fixed to the membrane, inhibit the normal functioning of the cell itself or the processes within the cell. Internal reactions also result when specific ions diffuse through the membrane and enter the protoplasm. Certain ions diffuse rapidly through a given protoplasmic membrane, others diffuse slowly, while still others do not diffuse through the membrane at all. This selective permeability is dependent upon the physicochemical structure of the outermost and innermost layers of the membrane. Normal permeability can be changed by some drugs which alter the membrane potential, thereby increasing or reducing the permeability; this results in an upset of the normal metabolism of the cell.[6]

The influence of pH is illustrated by the action of silver and mercury on the enzyme saccharase. The concentration of Ag^+ required to produce 50 per cent inhibition of saccharase is 25 times greater at pH 4.2 than it is at pH 6.1, whereas the activity of Hg^{++} decreases as the pH increases. This is to say that the mercuric ion is most effective in a strongly acidic medium, while the silver ion is most effective in a weakly acidic medium.[7]

Recently, a new interpretation of drug action has come into prominence in special instances, namely, the principle of a foreign substance competing with a naturally occurring protoplasmic substance for position in an enzyme system. As a rule, the two competing substances are generically related, or at least of similar structure. This principle has been demonstrated in the field of organic chemistry by the systems: (1) para-aminobenzoic acid and sulfanilamide (or its derivatives) and (2) histamine and antihistaminics.

INCOMPATIBILITIES

The science of chemistry is concerned with the physical and chemical properties of matter. Presumably, a student who is very well versed in chemistry should encounter no difficulty with incompatibilities which are associated with the physical or the chemical properties of compounds. However, the average student frequently fails to correlate incompatibilities with the basic principles upon which they are founded, and as a result he regards them a separate field of study. One of the primary functions of pharmaceutical chemistry lies in reconsidering general physical and chemical reactions in a manner which trains the student to analyze the reactions and which enables him to predict, as well as to detect, incompatibilities.

Incompatibility can be defined as the inability of a substance to maintain its identity or to exercise its inherent properties when it is brought into contact with or into the sphere of influence of another substance or a physical force. Thus, when sulfuric acid is added to water, heat is evolved; when potassium iodide is dissolved in water, heat is absorbed from the surroundings. These reactions, the former exothermic and the latter endothermic, represent incompatibilities of a secondary order; chemical reactions occur with the formation of the corresponding hydrates of sulfuric acid and potassium iodide along with an exchange of energy. When sodium hydroxide solution is added to hydrochloric acid solution, no visible reaction takes place in the absence of an indicator, no detectable amount of heat is given off if the concentrations are low enough, yet a chemical reaction takes place, representing the incompatibility of the acid and the base. If a solution of potassium bromide were added to a solution of zinc sulfate, no perceptible chemical or physical reaction would occur, and the two salts are regarded compatible. Yet, according to the theory of electrolytic dissociation, this equilibrium results:

$$\begin{array}{rcccc}
2KBr & \rightleftharpoons & 2K^+ & + & 2Br^- \\
 & & + & & + \\
ZnSO_4 & \rightleftharpoons & SO_4^{--} & & Zn^{++} \\
 & & \updownarrows & & \updownarrows \\
 & & K_2SO_4 & & ZnBr_2
\end{array}$$

Generally, this is overlooked, for while it is true that there is a mutual exchange among the ions, the existence of a reaction is ignored.

From the point of view of the pharmacist, all incompatibilities fall into two classes, namely, the desirable and the undesirable. Granular effervescent salts and water represent the former, while ferrous iodide syrup and air represent the latter. To be sure, there are many illustrations of both types, and it is not unusual to find the same illustration listed under both headings, depending upon the circumstances.

For the purpose of classification, three categories of incompatibilities are recognized generally. The different kinds are listed under the respective headings, and simple illustrations are offered.

Physical incompatibilities are those which emanate from the physical properties of compounds. In addition, there are several types of chemical incompatibilities which result from the influence of physical forces on compounds. Their classification under the physical or chemical heading is arbitrary. The following are listed as factors in physical incompatibilities:

1. *Insolubility*—The precipitation of sodium chloride from aqueous solution by the addition of alcohol.

2. *Immiscibility*—An oil and water.

3. *Heat*—In addition to the physical changes which it produces, heat is an important factor in the decomposition of many compounds. The physical changes include evaporation, melting, subliming and boiling. Illustrations are the evaporation of solid carbon dioxide, eutectic mixtures, the sublimation of iodine and the fractionation of liquid air.

4. *Pressure*—Since it is associated with heat, the incompatibilities which are dependent upon pressure are closely allied to those which are dependent upon heat. Mercury ointment can be triturated lightly without apparent change; however, if pressure is applied to the pestle, the heat developed by friction presumably softens the ointment base and the mercury globules coalesce.

5. *Cold*—The abstraction of heat causes liquids to congeal or to crystallize, as in the case of olive oil, acetic acid and saturated solutions.

6. *Light*—Through a physical force, light serves as a stimulus for many chemical reactions. The discoloration of sodium iodide solutions, the bleaching of dyes and the photosensitivity of the silver salts illustrate this kind of incompatibility.

7. *Percussion*—Violent reactions may result from the trituration of mixtures of seemingly harmless chemicals. The combination sulfur, charcoal and potassium chlorate is one of these mixtures.

Chemical incompatibilities seemingly outnumber the physical type. Every type of chemical reaction belongs to this group, however, only the common ones will be offered in illustration.

1. *Hydrolysis*—Water causes the decomposition of many inorganic chemicals, for example, arsenous iodide and sodium perborate.

2. *Condensation*—A common reaction between acids and bases.

3. *Oxidation*—These reactions range from the mild type, as in the case of ferrous iodide, to the violent type, associated with the hypophosphites and other powerful reducing agents.

4. *Reduction*—The reduction of mercury compounds through contact with iron utensils and the vigorous reduction of potassium permanganate illustrate extremes in this type of reaction.

5. *Precipitation*—Numerous double decomposition reactions, to say nothing of the other kinds of chemical reactions, result in the separation of insoluble reaction products.

6. *Gas evolution*—Dangerous incompatibilities in prescriptions arise from the liberation of a gas from a chemical reaction. Carbon dioxide and ammonia are among the gases commonly encountered.

7. *Heat liberation*—Among the exothermic reactions, condensations are foremost because of the energy liberated in the formation of water. Heat of solution and/or heat of hydration is liberated when compounds like strong mineral acids, caustic alkalies or stannic chloride are combined with water.

8. *Heat absorption*—True endothermic reactions do not proceed in the absence of energy from the outside. However, some compounds, like potassium iodide and sodium thiosulfate, cause a marked lowering

of temperature when they are dissolved in water.

Physiologic incompatibilities are not a part of pharmaceutical chemistry, yet they are of no less importance than those already mentioned. They are considered here in order to complete the pattern. This type of incompatibility, which is far less frequent than either the physical or the chemical type, occurs within the living organism when two or more substances whose physiologic actions are directly opposite are brought together within a given tissue. It is necessary merely to mention some of the classes of drugs which are physiologically incompatible: (1) stimulants and sedatives, (2) mydriatics and myotics, (3) pyretics and antipyretics and (4) vasoconstrictors and vasodilators.

Just as two compounds can be antagonistic physiologically, so can other combinations support each other; in the latter case the net result is greater than the simple sum of the individual reactions. Such is the case with synergists, or synergistic compounds. These are illustrated by: (1) sodium borate and boric acid, (2) mercurials and salicylates and (3) mercurials and halides.

It is not the purpose of this text to provide extensive discussion of incompatibilities, however, the foregoing should serve to convince the average student that the answers to many of these problems already lie within his comprehension—in fundamental chemical reactions. The order of compounding prescriptions frequently is designed for the specific purpose of avoiding or overcoming incompatibilities. It is the obligation of the pharmacist to recognize these problems, to avoid them when possible and to overcome them when necessary.

POISONS AND ANTIDOTES

The consideration of antidotes for poisons becomes greatly simplified when one understands incompatibilities. Other than the stomach pump and emetics, the devices (whether physical or chemical) used in the treatment of poisoning are based on incompatibilities; the substance or factor responsible for the poisoning is counteracted physically, destroyed or rendered inert chemically or opposed physiologically.

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2
The Periodic Table

INTRODUCTION

Too often do students successfully complete the work in general inorganic chemistry without an adequate appreciation of the significance and the value of the periodic table and its implications. The periodic table will be found to be of immeasurable value, both in retrospect and in anticipation of further work in chemistry. It should be understood from the very beginning that the periodic classification of the elements is not a man-made device. Instead, it is a natural phenomenon discovered by man. This is evidenced by the fact that the original title was "The Natural System of the Chemical Elements." Furthermore, it should be understood that the discovery of the system did not result from the efforts of any one man. Mendeléeff, whose name is assigned to the table which we now use, stated, "I have studied their [his predecessors and contemporaries] researches and they arouse me to seek for a true law." [1]

Like chemistry itself, pharmaceutical chemistry treats with two categories of matter, namely, inorganic and organic. The inorganic group can be subdivided into:

1. Elements
2. Compounds
   a. Acids (and oxides)
   b. Bases (and oxides)
   c. Salts

An element is defined as a substance which cannot be broken down into a simpler substance by chemical means. All compounds are composed of elements.

An acid can be defined in various ways: (1) a donor of protons, (2) an acceptor of electrons and (3) a source of hydrogen ions. A base, likewise, can be defined as: (1) an acceptor of protons, (2) a donor of electrons and (3) a source of hydroxyl ions.

A salt is considered to be the condensation product of an acid and a base. (For another interpretation, see p. 20.)

Inasmuch as work with chemicals is based upon elements and compounds of elements, it is obvious that an understanding of the elements is of primary importance. The people of ancient civilizations used elementary substances which were readily available to them. They were used for jewelry, coinage, utensils and construction. The Old Testament of the Bible and ancient history in general make frequent reference to gold, silver, copper, iron, lead, tin, mercury, sulfur and carbon. Of course, the people did not recognize the elementary nature of these substances. The ancient Greek philosophers believed that all matter consisted of a single primary substance, but they were not in agreement over the identity of the primary substance. Thus, Thales believed that it was water, and Heraclitus believed fire to be the one fundamental material. The contention

of Empedocles (440 B.C.) that all matter consisted of air, earth, fire and water held for many centuries.[3] Despite the fact that some primary substances were known and others were discovered in the interim, Paracelsus,* the father of iatrochemistry, contended that there were but three elements, namely, sulfur, mercury and salt. Throughout the eras of belief in iatrochemistry and phlogiston, numerous elements were isolated; nevertheless, it was not until the beginning of the nineteenth century that scientists (physicians, pharmacists, physicists and chemists) became genuinely interested in the possible existence of some kind of relationship between the elements.

Like the early Greek philosophers, Dalton regarded the atom as a small, hard, indestructible particle of matter which was the simplest building stone of nature. Furthermore, he assumed all atoms to be alike, consequently his curiosity was aroused when, in 1803, he observed that a given quantity of water did not dissolve equal volumes of all gases. The inconsistency was attributed to the relative weights of the ultimate particles. He determined the weights and compiled what frequently is referred to as the first attempt at a table of atomic weights.[3] This assignment of priority is incorrect, however, because Dalton's table included the molecular weights of gaseous compounds along with the atomic weights of elements in the gaseous state. The confusion is understandable because it was not until 1811 that Avogadro differentiated between atoms and molecules. The atom was defined as the smallest quantity of an element which can enter into a chemical reaction. A molecule was regarded the smallest quantity of a substance which possesses all of the specific properties of that substance.

* Paracelsus (his full name was Philippus Aureolus Paracelsus Theophrastus Bombastus von Hohenheim) (1498-1541) was a Swiss physician and teacher who was largely responsible for freeing medicine and chemistry from the snare of alchemy during the first part of the sixteenth century. He was an antagonist of the alchemists and believed it was the duty of the chemist, not to transform the baser metals into gold, but rather to prepare chemicals and medicinals for human use.

ORIGIN OF THE PERIODIC TABLE

In 1815, Prout, a physician, suggested that atoms of all elements might be made up of different numbers of hydrogen atoms. Although this suggestion was not accepted at the time, it is largely vindicated today. In the same year, Berzelius published a table listing the atomic weights of 36 elements, but the figures were quite inaccurate. It is to Döbereiner † that credit is due for first drawing attention (1817) to striking relationships between the elements. He demonstrated that there were several groups of three elements, which he called triads, whose three members had similar properties and whose middle member had an atomic weight which was roughly the average of the weights of the other two members. For illustration he used the following triads:

Calcium	40
Strontium	87
Barium	137
Lithium	6.9
Sodium	22.9
Potassium	39

Based on the properties of chlorine, bromine and iodine and on the atomic weights of chlorine and iodine, Döbereiner predicted

† Johann Wolfgang Döbereiner (1780-1849), a German apothecary who almost exclusively on the basis of self-study became one of the best and most inventive chemists of his time. As professor of chemistry, pharmacy and technology at Jena he enjoyed the support of the great poet Goethe who was Prime Minister of the Grandduchy Laxvaria-Weimar to which Jena belonged. Döbereiner is best known to pharmacists for his work on percolation, his textbook on pharmacy and for his platinum tinderbox. He was the first to recognize and exploit the effect of catalysis in his tinderbox as well as in chemical reactions, especially in the oxidation of alcohols to aldehydes and acids and the oxidation of sulfurous to sulfuric acid, which formed the basis of the contact process for manufacture of the latter.

the atomic weight of bromine, shortly after it was discovered.[4]

A valuable contribution facilitating the determination of atomic weights was made by Dulong and Petit in 1819. Through a study of the elements of known atomic weight they discovered that when the atomic weight is multiplied by the specific heat of the element in the solid state the result, approximately 6.2, is virtually constant for all elements. The observation can be restated as:

$$\text{at. wt.} \times \text{specific heat} = \text{at. heat} = 6.2 \text{ cal.}$$

or

$$\text{at. wt.} = \frac{6.2}{\text{sp. heat}}$$

On this basis, Berzelius (1825) redetermined the atomic weights with great precision.

In the years immediately following, a number of excellent workers engaged in the revision of the atomic weights. Among them were Pelouze, Marignac, Erdman, Peligot, Dumas and Stas. Although further attempts were made to extend existing ideas of classification, *viz.*, the triads of Kremers, Gladstone's arrangement, Cooke's homologous series, Dumas' homologous series, etc., no great success was achieved until after 1858 when Cannizzaro established accurate atomic weights for all of the elements then known.

The mention of Chancourtois in the development of the natural system of the elements usually is associated with the telluric screw which he devised. It consisted of a vertical cylinder on which he placed the symbols of the elements at heights proportional to their atomic weights. On the cylinder, which was divided into 16 equal parts (atomic weight of oxygen), he traced (at an angle of 45° with the axis) a spiral which crossed a given perpendicular or generatrix at distances from the base which were multiples of 16. Thus, lithium, sodium and potassium fell on one perpendicular, while oxygen, sulfur and selenium fell on another. Chancourtois' greatest contribution resulted from his observations on the poorly appreciated telluric screw. He noted the great similarity existing between elements appearing on the same generatrix, and he mentioned the periodic recurrence of properties. His conclusion can be regarded as an inarticulate statement of the periodic law. He concluded that the properties of substances are the properties of numbers.[5]

The periodicity of properties was further observed by Newlands (1864). When he arranged the elements in the order of increasing atomic weights, he noticed that after each interval of eight elements similar physical and chemical properties reappeared. Thus, reference is made to Newlands' octaves.

THE NATURAL SYSTEM AND THE PERIODIC LAW

The climax in the development of the natural system began when Lothar Meyer, in 1864, published a paper on the nature of atoms and the basis for their relationship.[6] In his first table, which was incomplete, Meyer arranged the elements horizontally according to their atomic weights, so that analogous elements stood under one another, and the change in valence and atomic weight could be obtained easily. Certainly a genuine interest, and perhaps competition from other investigators, caused Meyer to publish revised and improved tables containing 56 elements, in 1868 and 1870.

Though he was engaged in the study of the elements at this time, little was heard of Hinrichs, who utilized recent developments in spectroscopy to aid in his investigations. In 1866 he made the remarkable statement that the properties of chemical elements are functions of their atomic weights. The statement seems all the more remarkable when one realizes that it was issued three years before Mendeléeff an-

nounced the same relationship as his periodic law.

Mendeléeff was not disposed to ignore the efforts and the contributions of other investigators. As a matter of fact, he made the statement which already has been quoted, but which may well be repeated, "I have studied their researches and they arouse me to seek for a true law." Nevertheless, he denied Lothar Meyer any part in his discovery which was in the form of a classification of the elements published in 1869 under the title, "On the Relationship of Properties to the Atomic Weight of the Elements." [7] The short paper is summarized adequately in Mendeléeff's own statement that the elements, if arranged according to their atomic weights, exhibit an evident periodicity of properties. Far more remarkable than either Mendeléeff's first table or the conclusion based on it (already stated by Chancourtois and Hinrichs) is the fact that he ventured to predict the existence of elements not yet isolated.

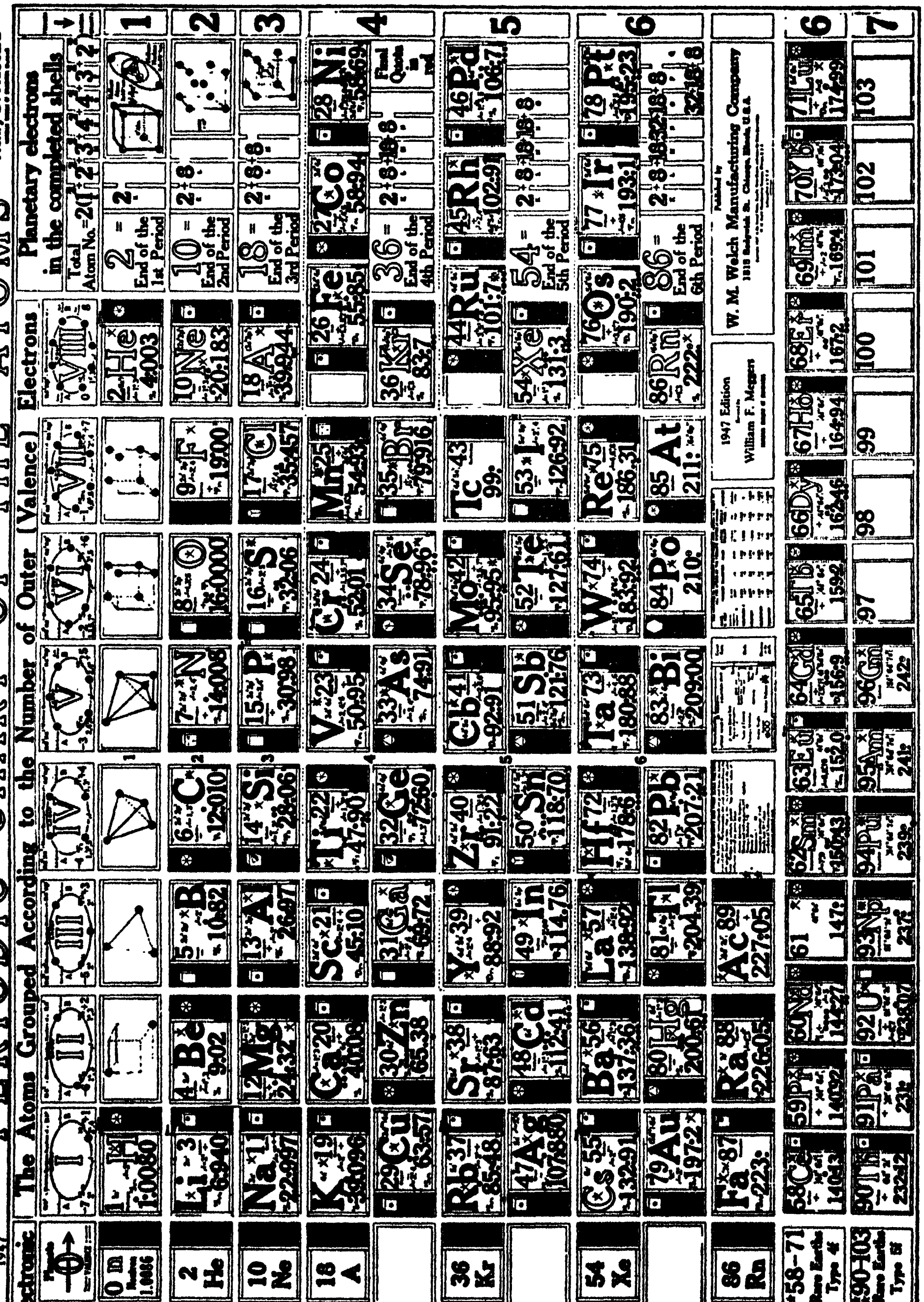
In a second paper,[8] presented before the Russian Chemical Society in 1869, Mendeléeff elaborated considerably on the relationship of the properties of elements to their atomic weights. In 1871 he offered a greatly revised table in his report on the periodic classification of the chemical elements.

Though they worked independently, simultaneously and apparently somewhat at odds with each other, the interpretations of Mendeléeff and Meyer are co-ordinated in the modern periodic table or classification of the elements. (See Fig. 1 for the periodic table of the elements.) Their efforts, together with those of the many other scientists of the era, provided the periodic law, which stated that the properties of the elements are periodic functions of their atomic weights.

In the years immediately following Mendeléeff's announcement, there was an apparent letdown in researches concerning the elements, perhaps primarily because the two most prominent figures gave their attention to other problems. Mendeléeff undertook the investigation of petroleum, and Meyer was busily attempting to classify organic chemicals on a basis similar to that developed for inorganic chemicals. In later years, Meyer continued to work on the table; however, it is most remarkable that Mendeléeff's interest in the phenomenon diminished considerably. It was pointed out to him that his arrangement of the elements was not always rational and that sometimes they were grouped according to their properties even though this resulted in a reversal of the order of increasing atomic weights. Instead of seeking the correct answer, Mendeléeff replied that these discrepancies in all probability were due to inaccuracies in the atomic weights. Illustrations of these irregularities wherein the order of increasing atomic weights was not followed include these pairs of elements: (1) argon and potassium, (2) tellurium and iodine and (3) cobalt and nickel.

INTRODUCTION OF OTHER FACTORS CONTRIBUTING TO A BETTER CLASSIFICATION OF THE ELEMENTS

It is most likely that the letdown was only apparent and not actual, for, as a matter of fact, the discovery of gallium and scandium, as predicted by Mendeléeff, aroused a tremendous amount of interest and brought added prestige to the periodic law. Yet, men were not satisfied with the table as presented and they sought to correlate atomic weight, atomic density, atomic volume, physical and chemical properties in the hope of perfecting a system of classification. Their interest in the composition and the genesis of the elements was revived and they sought to explain the forces which held together the parts of the atom and the molecule. Prout's theory that the elements were made up of different numbers of hydrogen atoms never did die, but it was



PERIODIC CHART OF THE ATOMS
The Atoms Grouped According to the Number of Outer Electrons (Valence)
Planetary electrons in the completed shells
Revised Edition 1947
Henry D. Hubbard
W. M. Welch Manufacturing Company
1947 Edition
William F. Meggers

FIG. 1.

severely challenged. As a matter of fact, the periodic law was restated in 1888, based somewhat upon this premise.[9] Hartley defined the atomic weight of an element as the ratio of the mass of its atoms to the mass of an atom of hydrogen. The periodic law was then stated as follows: "The properties of the atoms are a periodic function of their masses."

Marggraf (1758) observed that the burning of sodium compounds produced a yellow flame, while potassium compounds imparted a violet color to a flame.[10] Wollaston's examination of the spectrum of a candle flame through a prism, in 1802, perhaps marked the beginning of spectrum analysis. The interpretations and the applications of this technic were advanced greatly through the efforts of numerous prominent physicists, including Fraunhofer, Brewster and Talbot, the latter of whom demonstrated how to distinguish between lithium and strontium with the aid of a prism. In 1854 David Alter showed that each element studied had its own spectrum,[10] and this discovery, combined with the invention of the spectroscope by Bunsen and Kirchhoff, inaugurated an era of spectroscopic examination of matter. The combination of the discoveries was extremely important because it provided investigators with a new tool for analysis and identification. Hinrichs used the developments in spectroscopy to aid him in the investigation of the elements; he came to the conclusion which was stated previously, namely, that the properties of the chemical elements are functions of their atomic weights. Based upon his observations in spectrographic analysis, Gruenwald offered a most significant definition of chemical atoms in 1888.[11] He defined a chemical atom as a complex of exceedingly many movable particles which are elastic but so intimately connected that no known chemical process is capable of severing this union and breaking the atom into fragments. A suggestion as to the identity of this force which held the particles together might have been gathered from Davy's and Berzelius' interpretation of the electrical nature of matter. The basis for the modern interpretation of the structure of the atom was offered by these two men. Davy contended that in a compound, the atoms of the different elements acquire opposite charges by contact and thus mutually attract each other. Davy's electrochemical theory was superseded by that of Berzelius in 1807. According to the theory of the latter, every atom is charged with both kinds of electricity, which exists upon the atoms in a polar arrangement, the electrical behavior of the atom being determined by the kind of electricity which is in excess.[11]

The concepts of atomic structure were advanced greatly during the latter part of the nineteenth century and the early years of the twentieth. The isolation of the rare gases by Rayleigh and Ramsey and the discovery and study of the radio-active elements by Becquerel, Pierre and Marie Curie, Crookes and others furnished experimental evidence which Lord Rutherford employed to great advantage in explaining the structure of the atom. He compared the atom with a planetary system which revolved about a nucleus. He believed that a given atom should consist of equal numbers of protons and electrons and that all of the protons were contained in the atomic nucleus. As a result of his "scattering" experiments, he concluded that only a portion of the electrons were in the nucleus, and he demonstrated means of determining the number of free protons in the nucleus. The specific answer to the question of how many electrons were in the nucleus was furnished in 1913 by Moseley, who studied the x-ray absorption spectra of the elements. By the use of x-ray tubes in which cathode rays were impinged upon a target consisting of a given element, he was able to show that a definite arithmetic progression existed in the lengths of the waves emitted and that order numbers could be assigned to the elements. These order numbers have been

designated atomic numbers (Moseley numbers). Subsequent work on electron measurements by Millikan and on the hydrogen atom by Bohr has added immensely to the understanding of atomic structure.

Moseley's determination of atomic numbers provided a new means for the classification of the elements. While the new arrangement is not much different from Mendeléeff's classification on the basis of atomic weights, the discrepancies in Mendeléeff's table are for the most part overcome. Consequently, and as will be shown later, it is best to redefine the periodic law as follows: "The properties of the elements are the periodic functions of their atomic numbers."

ATOMIC STRUCTURE

In order to complete the understanding of the differentiation between atomic weight and atomic number, it is necessary to give a brief description of atomic structure. Atoms are assumed to consist basically of protons and electrons. The proton bears one unit of positive electricity and the electron bears one unit of negative electricity, and since all atoms are neutral in charge, there must be equal numbers of electrons and protons. The proton is a tiny but heavy particle, having a mass of 1.008 atomic weight units (practically the same mass as the hydrogen atom), while the electron is 1/1,838 of the proton mass. It is estimated that if a proton were as large as a pin head, the pin head taken on the same scale would be as large as the sun (linear diameter 864,000 miles). Based on Rutherford's work, it is understood that all of the protons and some of the electrons form the nucleus of the atom and that the remaining electrons are in a constant state of motion in fixed orbits around the nucleus (Fig. 2). These non-nuclear electrons are referred to as planetary electrons.

As an example, consider potassium (Fig. 3). This element has an atomic weight of 39.096, indicating that it is composed of 39 protons and 39 electrons. Its atomic number, 19, furnishes the key to the picture of the atomic structure of potassium. We know that there are 39 protons in the nucleus and that 19 of the electrons are planetary. The

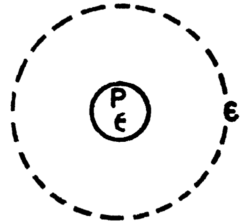


FIG. 2. P is numerically equal to the sum of ε nuclear and ε planetary. Being of opposite charge, the protons and the electrons in the nucleus are very closely associated, forming neutrons (1 P + 1 ε) or particles with a neutral charge. Since the number of protons in the nucleus exceeds the number of electrons in the nucleus, there remains an excess of protons after as many neutrons as possible have been formed. The neutrons and the excess of protons become associated in the proper numbers to form as many alpha particles (α) as are possible. The alpha particle, which consists of 4 protons and 2 electrons or of 2 neutrons and 2 protons, is recognized to be identical with the helium nucleus or the helium ion.

difference between 39 and 19, or 20, represents the number of electrons in the nucleus. Because of their affinity for each other, the protons and electrons in the nucleus combine to form various nuclear particles. Thus, 39 protons and 20 electrons are the equivalent of: (1) 19 neutrons and 20 protons (left over) or (2) 9 alpha particles, 2 neutrons and 1 proton (left over).

It was mentioned previously that the planetary electrons revolve about the nucleus at a constant rate, in fixed orbits. Hydrogen and helium are the only elements whose atomic structure shows only one orbit. Other elements have two, some have three, and so on to uranium which has eight orbits. The number of orbits which an element has indicates the period (or the horizontal group in the periodic table) to which

the element belongs. The orbits represent electron energy levels, with the innermost orbit representing the lowest energy level and the outermost representing the highest energy level. When, by electron bombardment, an electron is caused to move from a lower to a higher energy level, the atom is said to be excited and in that condition it possesses potential radiant energy.

Potassium, with 19 planetary electrons, marks the beginning of the fourth period. That is to say it is the first element (taken in the order of increasing atomic numbers) to have its planetary electrons arranged in four orbits, as shown in Figure 4.

One of the assumptions made by Dalton in his atomic theory was that all atoms of a given element are identical. However, modern investigations of atomic structure prove that this assumption is not entirely true, and that indeed it is true for only a small number of elements. For example, investigation has shown that there are actually two kinds of potassium atoms. They occur to-

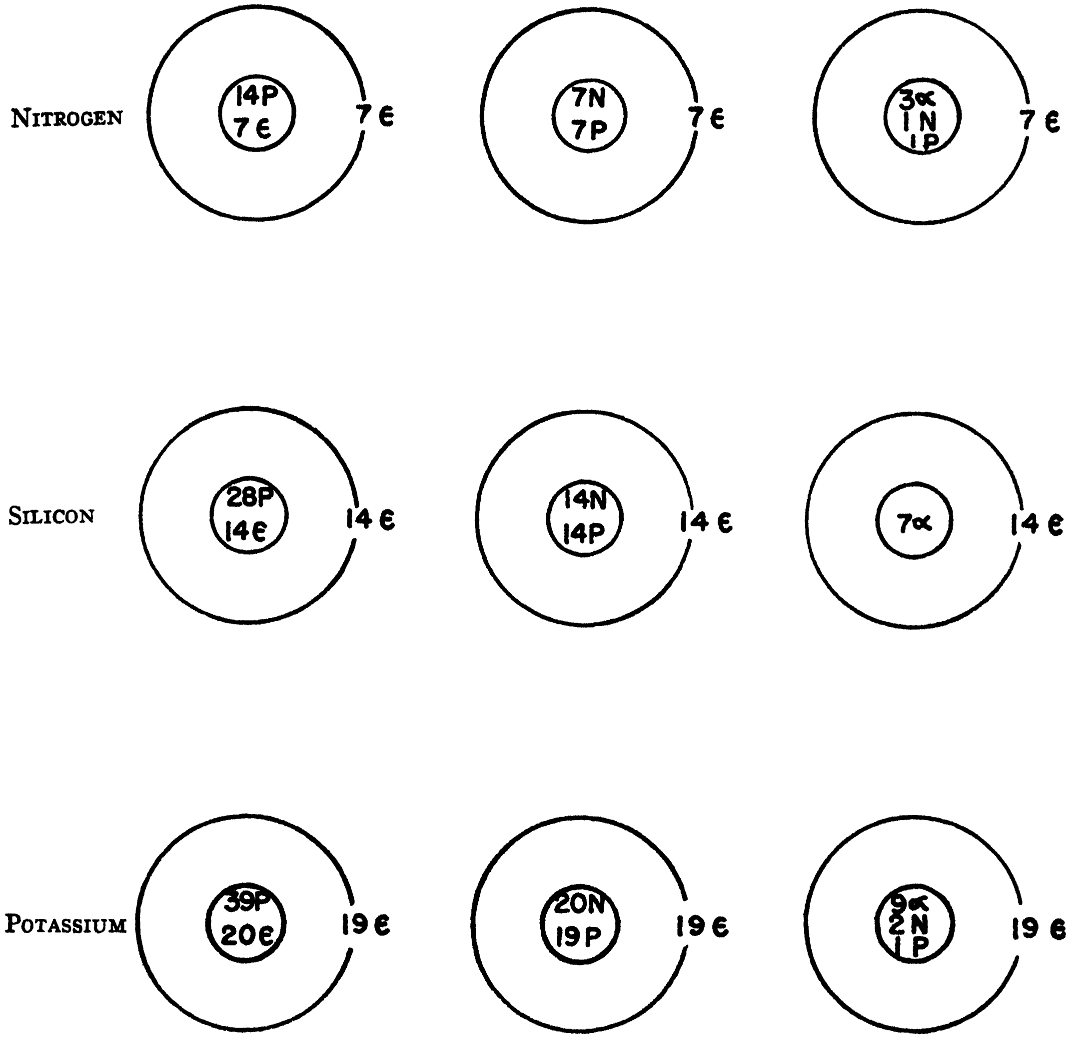


FIG. 3. The several methods of indicating grossly the atomic configuration of nitrogen, silicon and potassium.

gether in a fixed proportion, their atomic numbers and their chemical properties are identical, but their atomic weights are 41 and 39 respectively. Since their atomic number is 19, this indicates that one kind of

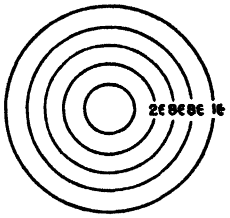


FIG. 4. Diagrammatic representation of the structure of the potassium atom.

atom (at. wt. 41) has the structure: 41 protons and 22 electrons in the nucleus and 19 planetary electrons while the other kind of potassium atom (at. wt. 39) has the structure: 39 protons and 20 electrons in the nucleus and 19 planetary electrons.

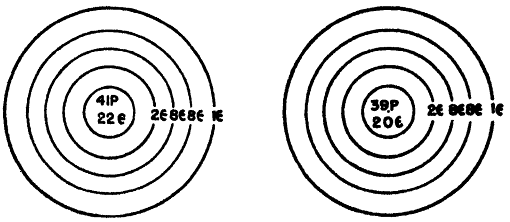


FIG. 5. Isotopes of potassium.

Atoms whose atomic numbers are the same but whose atomic weights (masses) are different, are called isotopes (see Fig. 5). Magnesium has four isotopes, aluminum has one, mercury has seven, etc. For the sake of uniformity, it is necessary that a standard atomic weight be adopted for each element. The atomic weight which is customarily given for each element actually is the proportionate average of the atomic weights of the isotopes of that element. This explains why the atomic weights are not expressed by whole numbers.

VALENCE

In order to construct the formula for a compound and to complete equations illustrating chemical reactions, it is necessary to understand valence relationships. Valence is a measure of the combining power of an element, a function of outer orbit electrons. This concept is based on an intensive study of the atomic configuration of the inert gases.

The inert gases (helium, neon, argon, krypton, xenon and radon) are outstanding among the elements in that they do not enter into chemical combination. Reactions for and compounds of the inert gases are not known. If it is accepted that a chemical reaction results from instability in a given system, it can be concluded that the inert gases represent the most stable atoms known to exist. The parallel in the stability of the gases suggests a parallel in their atomic configurations (Table 1). X-ray studies have shown that the relationship exists in the highest energy levels of the extranuclear electrons. Like all other atoms, the atoms of the inert gases are composed of protons and electrons; however, in their outer orbits the atoms of the rare gases (with the exception of helium) have 8 electrons. Therefore, it is concluded that the most stable atoms are those which have 8 electrons in the highest energy level. In this group, helium is exceptional because with the atomic number two, the helium atom can have only two planetary electrons, both of which are in the same orbit.

It is a natural tendency for any system (in the absence of an outside force) to orient itself in such a manner as to provide for the greatest stability within the system. This accounts for the ability of atoms to enter into chemical reactions and chemical combinations. In other words, when atoms are brought together, there is a reorientation or a redistribution of the outer orbit electrons so as to attain a structure similar to that

TABLE 1. DISTRIBUTION OF PLANETARY ELECTRONS IN THE INERT GASES

Name	Symbol	Atomic Number	Energy Levels of Planetary Electrons					
			First	Second	Third	Fourth	Fifth	Sixth
Helium..........	He	2	2	..	..	..	..	..
Neon...........	Ne	10	2	8	..	..	..	..
Argon..........	A	18	2	8	8	..	..	..
Krypton........	Kr	36	2	8	18	8	..	..
Xenon..........	Xe	54	2	8	18	18	8	..
Radon..........	Rn	86	2	8	18	32	18	8

of the inert gases. This may be attained by one of three methods, namely:

1. an atom may lose electrons to another atom or other atoms,
2. an atom may gain electrons from an-another atom or other atoms,
3. an atom may share electrons with an-another atom or other atoms which also are seeking stability.

The method by which the stable structure is attained is that method which involves the least expenditure of energy.

These points are best illustrated through the use of modified common symbols in which the symbol for an element is interpreted to represent all of the atomic configuration of that element except the outer orbit electrons. The electrons of the highest energy level are represented individually by dots placed about the symbol (Table 2).

TABLE 2. DISTRIBUTION OF PLANETARY ELECTRONS IN CERTAIN ELEMENTS

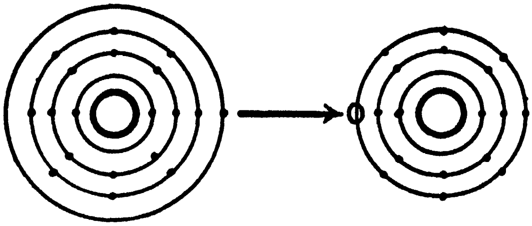
Symbol	Atomic Number	Planetary Electrons			Modified Symbol
		Innermost Level	Intermediate Levels	Outermost Level	
Na.........	11	2	8	1	$\mathrm{Na}\cdot$
K..........	19	2	8 8	1	$\mathrm{K}\cdot$
Ca.........	20	2	8 8	2	$\mathrm{Ca}:$
S..........	16	2	8	6	$:\ddot{\mathrm{S}}:$
Cl.........	17	2	8	7	$:\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}\cdot$

When potassium and chlorine are brought together, they react to form the compound potassium chloride. The reaction occurs as a result of the fact that potassium gives up its one electron in the highest energy level to chlorine, which needs only one electron to go with the seven in its highest energy level, thereby giving chlorine eight electrons in its outermost level. As a result of this loss and gain of electrons, potassium now has eight electrons in its outermost level, chlorine has eight in its outermost level and

both potassium and chlorine now have the same electronic arrangement as the inert gas, argon (Fig. 6).

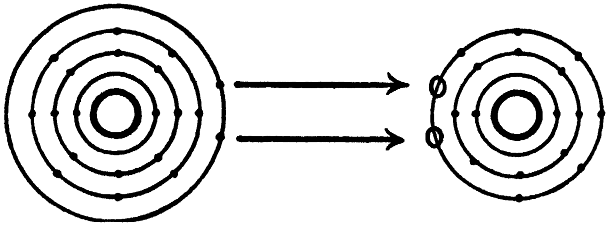
Figure 7 represents the distribution of electrons when atoms of calcium and sulfur combine to form calcium sulfide.

The transfer of electrons, as demonstrated, gives rise to electrovalence. Positive electrovalence results from the loss of electrons and it is numerically equal to the number of electrons lost. Thus, potassium in potassium chloride has a valence of +1, and calcium in calcium sulfide has a valence of +2. Generally, the maximum positive valence of an atom is indicated by the number of electrons in the outermost energy level. Negative electrovalence results from the gain of electrons and is numerically equal to the number of electrons gained. Thus, the valence of chlorine in potassium chloride is −1, and the valence of sulfur in calcium sulfide is −2. Generally, the maximum negative valence of an atom is represented by the difference between the number of valence electrons and eight. However, it is not always possible to predict maximum negative valence on this basis, as is shown in Figure 8.



POTASSIUM CHLORINE

FIG. 6. Distribution of electrons when potassium and chlorine combine to form potassium chloride.



CALCIUM SULFUR

FIG. 7. Distribution of electrons when calcium and sulfur combine to form calcium sulfide.

The approximation of the inert gas structure by the sharing of electrons is demonstrated in the sharing of electrons by two chlorine atoms, thus:

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:$$

A stable configuration for carbon tetrachloride cannot be derived by the loss or gain of electrons. The configuration of the inert gases is approximated by the sharing of electrons.

$$\begin{array}{c} :\overset{\cdot\cdot}{Cl}: \\ \cdot\times \\ :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}{}_\times^\cdot C{}_\times^\cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \\ \cdot\times \\ :\underset{\cdot\cdot}{Cl}: \end{array}$$

The type of bond formed when two atoms combine in such a manner that each atom

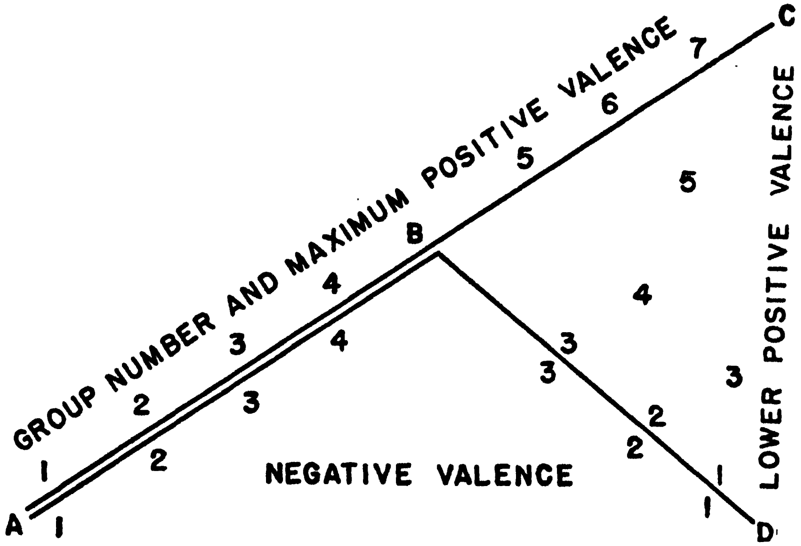


FIG. 8. Prediction of valence.

furnishes one electron of a shared pair is referred to as covalence.

In some instances, instead of each of the two atoms furnishing one electron of the shared pair, one atom may furnish both electrons of the shared pair. This type of chemical bond, referred to as co-ordinate valence, is illustrated in sulfur dioxide, chlorine and water.

$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{}^{\circ}_{\circ}\overset{\circ\circ}{\underset{\circ\circ}{S}}{}^{\circ}_{\circ}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}: \qquad H{}^{\cdot}_{\circ}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{}^{\cdot}_{\circ}H$$

It is not necessary to elaborate further on the concept of valence; it is more advantageous to simplify the association of valence with the periodic table.

There are numerous interpretations of the periodic table; each has merit and all of them have inherent weaknesses. One of the greatest and most common of the weaknesses is that the table tends to emphasize the maximum positive valence of the elements, with little or no mention of the lower valences. The maximum positive valence is most readily apparent when one lists the oxides of the elements in a given period, e.g.,

Group	Oxides
I	Na_2O
II	Mg_2O_2
III	Al_2O_3
IV	Si_2O_4
V	P_2O_5
VI	S_2O_6
VII	Cl_2O_7

In this list, the oxygen subscript corresponds with both the maximum positive valence for the electropositive element and the number of the group where the element occurs in the periodic table. It seems that the group number for an element generally indicates its highest positive valence. This fails to hold true in a surprisingly small number of instances, among which are copper and gold, both of which show positive valence higher than 1, and the so-called transition elements (primarily iron, cobalt, and nickel), none of which has a valence of 8.

Since most of the elements have more than one state of valence, it would be convenient to have a simple means of indicating the several states of valence. The method proposed is not perfect by any means, yet

it is so generally applicable for the common elements that it serves as a very practical tool.

In the diagram (Fig. 8), the valences of the elements in the various groups can be observed readily. The figures ranging from 1 to 7 along the line ABC represent the maximum positive valences of the elements in the correspondingly numbered groups of the periodic table. The figures, 1 to 4 to 1, included in the angle ABD represent the negative valences of the elements in each of the respective seven groups. The scattered figures found in the angle CBD show the lower positive valences assignable to the elements in groups V, VI and VII.

From this diagram, the following valence patterns can be drawn:

1. The elements of group VII can have valences of plus 7, 5, 3, 1 and minus 1.
2. The elements of group VI can have valences of plus 6, 4, 2 and minus 2.
3. The elements of group V can have valences of plus 5, 3 and minus 3.
4. The elements of group IV can have valences of plus 4 and minus 4. (The diagram does not show positive bivalence, which members of this group can have.)
5. The elements of group III can have valences of plus 3 and minus 3. (Transition elements, Fe, Co and Ni, belong here so far as maximum positive valence is concerned.)
6. The elements of group II can have valences of plus 2 and minus 2.
7. The elements of group I can have valences of plus 1 and minus 1.

The following tabulation illustrates the valences of the elements in the various groups.

Group	Valence	Positive	Negative
I	1	$AgCl$	AgH
II	2	$CaCl_2$	CaH_2
III	3	BCl_3	BH_3
IV	4	CCl_4	CH_4
V	5	PCl_5	
	3	PCl_3	PH_3
VI	6	SCl_6	
	4	SCl_4	
	2	SCl_2	SH_2 (H_2S)
VII	7	HO_4Cl	
	5	HO_3Cl	
	3	HO_2Cl	
	1	$HOCl$	ClH (HCl)

It must be understood that while the pattern offered is widely applicable, it is not without exceptions, some of which are notable. Copper and gold usually are listed in group I, yet copper is strongly bivalent (++), and gold is strongly trivalent. Lead is listed in group IV, yet its tendency to be bivalent (++) is most pronounced. Nitrogen is perhaps the most outstanding exception to this kind of orientation. Occurring in group V, it would be expected to show valences of plus 5 and 3 and minus 3. Yet, the following oxides of nitrogen are well known:

Valence	Positive	Negative
1	N_2O	....
2	N_2O_2 ($2NO$)	....
3	N_2O_3	NH_3
4	N_2O_4 ($2NO_2$)	....
5	N_2O_5	....

In group VI, oxygen is the exception. It is extremely common in the divalent form, the tetravalent form (oxonium compounds) is accepted with skepticism and the hexavalent form is unknown. In group VII, fluorine and manganese are exceptional. Only monovalent fluorine (−) is known. Manganese commonly shows valences of 7 ($KMnO_4$), 4 (MnO_2) and 2 ($MnSO_4$). While these exceptions do exist, they are neither so numerous nor so prominent to render the generalizations useless.

Lothar Meyer [12] is credited with having been the first to use the periodic classification of the elements as an aid in teaching inorganic chemistry. Its use in the same capacity now is commonplace, because it simplifies and clarifies the teaching process.

It is customary to study the halogens as a group because they are so closely related, yet the same types of relationships can be shown to exist among the alkali metals (group I) and among the elements of group V or group II, etc. The advantage lies in studying the properties of the elements of a single group as a whole so that needless repetition can be avoided.

The pattern for the presentation of the material covered in this text has been drawn on the basis of the hydrides and hydroxides of the elements and the substitution products of the hydrides and hydroxides. Of all of the derivatives of the elements, the hydroxides (and the thiohydroxides) can be shown to be the most versatile for teaching purposes. The hydroxides of the metals are the bases, and the hydroxides of the nonmetals are the acids. The hydroxides of the metaloids, being amphoteric, can function as acids or bases, depending upon the circumstances. Substitution of the entire hydroxyl group by a nonmetal yields salts, and substitution of the hydroxyl hydrogen by a metal also yields salts. Complete dehydration of the hydroxides yields the oxides of the elements; the complete removal of hydrogen sulfide from the thiohydroxides yields the sulfides of the elements.

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3

Elements of Group VII

THE HALOGENS
HYDRIDES OF THE HALOGENS
HALIDES OF THE HALOGENS
THE NONHALOGEN ELEMENTS OF GROUP VII

THE HALOGENS

The members of this group are fluorine, chlorine, bromine and iodine. The first one, fluorine, is but little known in the free state. They are termed halogens (salt formers from the Greek *hal,* salt, and *genein,* to beget or bring forth) * because they form salts by direct union with the metals. Salts previously were considered as resulting from the union of an acid (the oxide of a nonmetal) with a base (the oxide of a metal).†

History. Chlorine was discovered in 1774 by Scheele ‡ during his investigation of the mineral pyrolusite when he treated the native manganese dioxide with muriatic acid. Scheele called the gas "dephlogisticated marine acid air" in accordance with the phlogiston theory.§ Since, according to the theory of the antiphlogistonists, all acids contained oxygen, muriatic acid was supposed to contain oxygen. The chlorine obtained by oxidation was regarded as oxidized muriatic acid,|| under which name it became

* The Greek word, *hal,* meaning salt, is found in a number of terms, notably geographic names of places where salt is found, e.g., Halle in Germany, Hallein in Tyrol. The Greek word, *genein,* is found in innumerable scientific terms of which the pharmacist must know the meaning, e.g., in names of elements: hydrogen (former of water), nitrogen (former of nitre), oxygen (former of acids). It is found in other terms: chromogen (former of color), antigen (former of antibodies), sapogenin (former of saponin), and even in trade names (dioxogen, collagen, fibrogen, nucleogen, etc.).

† According to the electrochemical views of Davy and Berzelius, every compound consisted of two parts which were electrically different and without which a chemical compound could not be formed. Berzelius developed his dualistic theory with compounds of oxygen—the acids, bases and salts. The metals combined with oxygen to form bases and nonmetals combined with oxygen to form acids. Thus the typical bases of that period were written as K_2O, potassa; CaO, lime; BaO, baryta, etc.; while the acids were written as SO_3, sulfuric acid; CO_2, carbonic acid, etc. Rouelle defined salts as the product of the union of an acid with a base, thus $K_2O \cdot SO_3$, sulfate of potassa; $CaO \cdot SO_3$, sulfate of lime; $BaO \cdot CO_2$, carbonate of baryta, etc.

‡ Karl Wilhelm Scheele was a Swedish apothecary (1742-1786) who made some of the most remarkable chemical discoveries of his time. He discovered chlorine, manganese, baryta, and, independently from Priestley, oxygen; by his isolation of benzoic, citric, tartaric, oxalic and gallic acids, among others, from both plant and animal sources he gave to future investigators methods and technics which were invaluable.

§ Hydrochloric acid previously had been discovered by Glauber, about 1658, when he observed the action of sulfuric acid on common salt; it was called by him "spirit of salt." Later Priestley, in 1772, isolated the HCl gas and named it "marine acid air" to indicate its origin from sea salt. The liquid also was known as muriatic acid.

|| The theory of phlogiston, which dominated chemistry during the latter part of the seventeenth and most of the eighteenth centuries, was largely the elaboration of an attempt by John Joachim Becher (1635-1682) and George Ernst Stahl (1660-1734), two German physicians, to explain the phenomenon of combustion. The fire-element, supposed to be present in all combustible substances and which escaped during combustion was named phlogiston by Stahl. Such substances as soot and sulfur were regarded as almost pure phlogiston because they left

official in the pharmacopeias of the early nineteenth century. Even after it had been demonstrated that chlorine was an element, and even after the discovery of iodine by Courtois * in 1811 in the ashes of sea plants and the excellent researches of Davy and Gay-Lussac † in 1815 showing iodine to be an element analogous to chlorine, Berzelius ‡ was prone to regard chlorine as an oxide of a hypothetical element. Bromine, discovered by Balard § in 1826 in the mother liquid of sea salt, for a long time completed the group of the elements termed halogens by Berzelius. These three elements formed one of Döbereiner's "triads," one of the forerunners of the modern periodic system of elements (p. 7). Fluorine was not isolated until 1887, when Moissan || made the successful experiment of electrolysis of hydrofluoric acid in apparatus not attacked by either hydrogen fluoride or fluorine.

The name chlorine was suggested by Davy in 1810 from the Greek *chloros* (a greenish yellow).¶ Iodine derives its name also from its vapors which are violet colored, from the Greek *iodes*, by means of which it was discovered. Bromine, however, received its name because of its odor, from the Greek *bromos* (a bad smell, a stench). Fluorine was named after its source, fluorspar, from the Latin *fluo* (I flow), which is used in the fluxing of ores.**

A fifth halogen, element 85 in the periodic table, formerly known as alabamine, was synthesized in 1940 by Corson, MacKenzie and Segré by bombarding bismuth with al-

very little residue when burned. Scheele realized that the chlorine discovered by him was, as we would say, HCl from which the hydrogen had been removed; but since Scheele was of the phlogiston school of thought and regarded hydrogen as pure "phlogiston," the logic of his name, "dephlogisticated marine acid air," becomes apparent. With the overthrow of the phlogiston theory by the work of Lavoisier (1770 to 1787) and his oxygen theory of combustion, Berthollet, who belonged to the antiphlogistic school, believed chlorine to be a compound of oxygen and hydrochloric acid and called it "oxygenated muriatic acid." The latter idea prevailed until about 1810 when Gay-Lussac and Thenard, along with Davy, showed the gas to be a simple substance, i.e., an element.

* Bernard Courtois (1777-1838), a French pharmacist who later became a manufacturer of saltpeter and soap, observed the vapors of iodine while experimenting with the mother liquid of sodium carbonate obtained by leaching the ashes of sea plants. He observed that purple vapors were evolved upon adding sulfuric acid to this concentrated mother liquid. Two French chemists, Desormes and Clement, reported his observation to the Paris Academy of Sciences in 1813; the elemental character of iodine later was fully established by Gay-Lussac and Davy.

† Louis Joseph Gay-Lussac (1778-1850) is possibly best known to students of elementary chemistry through his law of combination of gases by volume. Sir Humphry Davy (1778-1829) is known also for his work on the galvanic current and his use of it in the isolation of the alkali and alkaline earth metals.

‡ Joens (Johann) Jacob Berzelius (1779-1848), at one time professor of medicine and pharmacy at Stockholm, exerted a most profound and lasting effect on all branches of chemistry. As a teacher he had such distinguished pupils as Wöhler, Gmelin, Mitscherlich and others. He is best known for his experiments and views on electrochemistry, the atomic theory, his dualistic theory and for his contributions to analytical chemistry. His *Lehrbuch der Chemie* served as a pattern for many succeeding textbooks. Berzelius aptly has been named "the great generalizer" in the history of chemistry.

§ Antoine Jerome Balard (1802-1876) was a French pharmacist and professor at Montpellier on the Mediterranean where he had occasion to study the mother liquid from the manufacture of salt from sea water.

|| Henri Moissan (1852-1907), like the discoverers of the other three halogens, came from the ranks of pharmacy. Possibly best known for his electric furnace and for the production of artificial diamonds, he was for a time professor of toxicology at the Ecole superieur de pharmacie in Paris and later professor of mineral chemistry at the Sorbonne.

¶ Other words of importance to pharmacists are derived from the same Greek root, namely, chlorophyll, from *chloros* (green) and *phyllos* (leaf), the green color of the leaf. Such words as chloroform, etc., have nothing in common with the original meaning of the word chlorine, but merely indicate that chlorine is one of the elements composing it.

** The use of fluorspar in the fluxing of ores makes use of the chemical principle that an impurity lowers the melting point or fusing point of a pure substance. Thus, by mixing the ore with fluorspar, the ore flows more easily when heated.

pha particles. It is radioactive with a half-life of $7\frac{1}{2}$ hours, and the name astatine, symbol At, from the Greek word meaning unstable, has been proposed for it since it is the only halogen without stable isotopes.[1]

Occurrence. Because of their so-called strong affinity for other elements, the halogens are not found in the free state in nature. In the mineral kingdom all four halogens occur widely distributed in combination. Chlorides, however, predominate in quantity, particularly as sodium chloride, both in solution in sea water and salt springs and as rock salt deposits. Chlorides of potassium, calcium and magnesium, as well as their bromides, also are widely distributed. The native halides of the heavy metals, such as lead, iron and silver, are relatively insoluble, hence such halides as silver chloride, bromide and iodide, occur as minerals either as such or in isomorphous mixtures.

Many of the metallic halides are readily soluble and when deposited from sea water, are mostly washed away by surface or underground waters. A few places exist where these soluble salts have been preserved because they were protected by impermeable layers of clay. Such a place is Stassfurt, in central Germany, which has supplied a large part of the world's market with potassium chloride and other halides.*

Sodium and magnesium bromides occur in sea water, and the former occurs along with sodium chloride in the salt wells of Michigan, Ohio, West Virginia and other places in the United States. Magnesium bromide is found in the Stassfurt beds, and sodium bromide occurs in various places as a surface layer over the sodium chloride. With the accumulation of the mother liquids from which the chlorides have been deposited, the traces of bromides that accompany the chlorides are also concentrated and these mother liquids, like those accumulated from salt production in Michigan and elsewhere, are then used for the production of bromine (p. 24). Bromides of alkali and alkaline earth metals also occur in mineral springs, the waters of which are prescribed for their medicinal ingredients.

While chlorine and bromine occur widely in combination as simple halides, iodine is found chiefly in combination with sodium, potassium, magnesium and calcium, not only as iodide but also as iodate, in sea water and many mineral springs. The chief commercial source of iodine is crude Chile saltpeter, or caliche, $NaNO_3$, in which iodine occurs to the extent of about 0.2 per cent, mainly as sodium iodate and partly as sodium iodide. It is obtained from the concentrated mother liquids remaining from recrystallization of the saltpeter (p. 32). An important source of iodine in this country is the oil well brines of California.

Much less is known about the occurrence of the halogens in the vegetable kingdom. The accumulation of iodine in sea weeds, especially those of the genera *Fucus* and *Laminaria*, has been used in the past for the production of this element.† Whether the presence of iodine in organic and possibly inorganic combination has anything

* Sylvite, KCl, and carnallite, $KCl \cdot MgCl_2 \cdot 6H_2O$, are two of the most important mineral salts found in the salt beds at Stassfurt. Carnallite is heated in aqueous solution to break up the double salt, and the concentrated solution upon standing deposits impure potassium chloride, which is purified by recrystallization. The mother liquids then are used for the treatment of more carnallite, during which process the concentration of the more soluble magnesium chloride increases. Upon evaporation of these mother liquids, the latter crystallizes as the hexahydrate, $MgCl_2 \cdot 6H_2O$, from which the anhydrous salt may be obtained.

† Certain sea weeds growing in deeper waters store iodine in their tissues. These sea weeds are washed up by the gulf stream on the exposed coasts of France (Normandy), Ireland, Scotland and elsewhere, and the ashes of these weeds, known variously as kelp, varec, barilla, etc., were formerly commercial sources of iodine. The weeds, washed up during stormy spring months, were collected by the natives, allowed to dry during the summer months, and then burned in large heaps. The ash contains an average of 0.2 per cent iodine as iodides and iodates. If the fire is too hot, some iodine is lost by volatilization.

to do with past uses made of certain seaweeds for medicinal purposes remains conjectural; such plants as Fucus, N.F.V., (Bladderwrack) largely have disappeared from modern pharmacopeias.

Iodine is accumulated not only by marine plants but also by marine animals, e.g., sponges, oysters, codfish and others. Spongiae ustae (burnt sponge) were formerly an item of the materia medica (U.S.P. of 1850); while they no longer are used medicinally, other organic iodine compounds have been found in the thyroid gland and elsewhere and have found their way into modern materia medica, e.g., Thyroid and Thyroxin U.S.P. XIII. Indeed, the modern campaign against goiter is based on supplying patients, particularly children of school age, with iodine in one form or another because their food or the materials used in preparing food are deficient, e.g., salt which has been purified so highly that it has been deprived of all iodine occurring naturally with it, hence the use of iodized salt.

Chlorine, in the form of sodium chloride, plays an important role in animal physiology. The normal human body requires about 15 grams of sodium chloride daily; this must be supplied through animal or vegetable food or as a condiment. In the digestive tract, the salt is hydrolyzed into hydrochloric acid and sodium hydroxide, thus supplying the acidity of the stomach and the alkalinity of the small intestine, in other words, the media in which digestion of foods takes place.

Fluorine, likewise, apparently plays an important role in the animal kingdom, being found in the teeth and in the bones; extensive investigations of the role fluorine plays in the prevention of dental caries are being carried on at the present time, and the possible beneficial effects of the addition of traces of fluoride to municipal drinking water is the subject of much discussion.[2] In the mineral kingdom, fluorine is found in fluorspar, CaF_2, its early source and whence its name, also in cryolite, $AlF_3 \cdot 3NaF$, in Greenland. Minute traces also occur in sea water and in some mineral springs.

Of the four halogens, only bromine has not yet been shown to be of specific need for the animal organism.

Methods of Formation and Preparation.

I. Dissociation of Hydrogen Halides and Metallic Halides.

$$2HX \xrightarrow{\text{energy}} X_2 + H_2$$

$$2NaX \xrightarrow{\text{energy}} X_2 + 2Na$$

It was by the electrolytic dissociation of hydrogen fluoride that Moissan first isolated fluorine (p. 21).

$$2HF \xrightarrow{\text{energy}} F_2 + H_2$$

The electrical dissociation of hydrogen chloride commonly is employed as a lecture experiment to demonstrate Gay-Lussac's law of combination of gases by volume.

The use of heat will accomplish similar results. The dissociation temperatures reveal the increasing instability of the hydrogen halides with increasing atomic weight of the halogen concerned; thus, HCl dissociates at about 1,500° C., HBr at about 800° and HI at about 180°.

In like manner, the metallic halides may be dissociated:

$$2NaCl \xrightarrow{\text{energy}} Cl_2 + 2Na$$

This method for the commercial preparation of chlorine is used wherever electricity can be obtained cheaply, in other words, where there is natural water power, e.g., at Niagara Falls. The chlorine thus obtained is either used directly in the manufacture of other chlorine compounds or is liquefied and marketed in steel cylinders. In the electrolysis of a solution of sodium chloride for the production of chlorine, the anode and cathode must be separated in order to prevent the products of electrolysis from mixing. Various types of cells have been devised to accomplish this. These cells make

use of either a porous diaphragm or a nonporous diaphragm over a layer of mercury. In the latter type, the chlorine gas escapes at the anode, while the sodium is held by the mercury as sodium amalgam, which, on contact with water, yields sodium hydroxide and hydrogen, both of which are commercial by-products:

$$2NaCl \xrightarrow{\text{electrolysis}} Cl_2 + 2Na$$

$$2Na + 2Hg \rightarrow 2NaHg$$

$$2NaHg + 2H_2O \rightarrow 2NaOH + H_2 + 2Hg$$

If the anode and cathode were not separated, sodium hypochlorite (at low temperatures) and sodium chlorate (at higher temperatures) would result from the following series of reactions:

$$2NaOH + Cl_2 \rightarrow H_2O + NaCl + NaOCl$$

$$3NaOCl \xrightarrow[\text{energy}]{\text{electrical}} 2NaCl + NaClO_3$$

Use is made of these reactions in the manufacture of the metallic hypochlorites and chlorates (pp. 81, 84).

Bromine also may be prepared by a similar electrolytic process from the mother liquids of salt from wells or sea water (pp. 22, 29). These mother liquids contain metallic chlorides and bromides which, upon electrolysis, yield both chlorine and bromine. The chlorine, being more active than the bromine, displaces the latter from its salts and becomes fixed again as metallic chloride. When all of the bromine has been displaced, the chlorine gas begins to come off from the chlorides and the operation is stopped.

II. Breaking Down a Higher Halide to a Lower Halide and Free Halogen.

A. The original method of Scheele is recognized as depending on this reaction (p. 20):

$$MnX_4 \rightarrow MnX_2 + X_2$$

However, $MnCl_4$ is so unstable it is not kept in stock but is prepared, whenever wanted, by the action of hydrochloric acid on manganese dioxide:

$$MnO_2 + 4HCl \rightarrow MnCl_4 + 2H_2O$$

It was by this method that chlorine was prepared for the Chlorine Water of the U.S.P. in the revisions of 1860 to 1910, inclusive. In place of hydrochloric acid, sodium chloride and sulfuric acid can be used since they generate the acid desired (p. 41).

The same reaction is involved in the description of Manganese Dioxide N.F.[3] and was used in the test for identification of Hydrochloric Acid in the U.S.P. XII.[4]

Scheele's original method for the preparation of chlorine forms the basis of the Weldon process which found considerable application at one time for commercial manufacture of chlorine. In the manufacture of chlorine by oxidation of hydrochloric acid, a variety of oxidizing agents may be used, but pyrolusite ore is usually resorted to because of its cheapness and because the products resulting from its use may be used over again in the process. In the Weldon process, the manganous chloride yielded as a by-product is reoxidized to manganese dioxide for production of more chlorine.

B. A second example of this general method of formation and preparation is found in the break-down of ferric iodide to ferrous iodide and free iodine, as illustrated in the determination of ferric iron in some of the official assay procedures. In the assay of the N.F. Ferric Chloride Tincture, for example, an excess of potassium iodide and hydrochloric acid are added to a measured sample of the Tincture, and the liberated iodine is then titrated with N/10 sodium thiosulfate:[5]

$$6HCl + 6KI \rightarrow 6KCl + 6HI$$

$$2FeCl_3 + 6HI \rightarrow 2FeI_3 + 6HCl$$

$$2FeI_3 \rightarrow 2FeI_2 + I_2$$

$$2Na_2S_2O_3 + I_2 \rightarrow Na_2S_4O_6 + 2NaI$$

Examples of the qualitative applications of this method of formation of iodine are found in the U.S.P. and N.F. tests for iodide impurity in Bromine, Sodium Bromide and

other soluble bromides contained in the same editions, e.g., "Iodide—Add a few drops of ferric chloride T.S. and 1 cc. of chloroform to 10 cc. of a solution of Sodium Bromide (1 in 20), and shake the mixture: the chloroform does not acquire a violet tint."[6] The same reaction was used in earlier revisions of the U.S.P. as a test for identity of soluble iodides.[7]

III. Oxidation of Halides by Oxygen or Other Oxidizing Agents. This method involves thermochemistry, and a brief review of thermochemical terms and equations and the value and application of simple thermochemical data is desirable. Chemical change is always accompanied by a change in chemical energy, which usually is manifested by the evolution or absorption of heat. Chemical reactions in which heat is evolved are described as being *exothermic;* when heat is absorbed, the reaction is *endothermic.* Exothermic reactions naturally take place much more readily than do endothermic reactions, in which energy has to be supplied. Physical changes as well as chemical reactions are usually accompanied by thermal changes. Thus, the processes of melting or fusion of a solid and vaporization of a liquid are usually endothermic and absorb heat, while the reverse changes, solidification or freezing of a liquid and condensation of a vapor, are exothermic and evolve heat.

The *latent heat of fusion* of a substance is the amount of heat required to convert one gram of the substance in solid state into the liquid state at the same temperature. The *latent heat of vaporization* is the amount of heat required to convert one gram of a substance in liquid state into the vapor state at the same temperature. The ***heat of solution*** is the thermal change which accompanies the solution of a substance in sufficient solvent that the addition of more solvent causes no further thermal change. It may be either exothermic or endothermic and usually is stated in terms of calories per gram mole of the substance dissolved.

Heat of reaction is a term used to denote the thermal change which accompanies a chemical reaction. The *heat of formation* of a compound is the thermal change which accompanies the formation of that compound from its elements. It may be either exothermic or endothermic and is usually stated in terms of calories per gram mole of the compound formed. Other commonly used thermochemical terms include *heat of neutralization, heat of combustion,* etc.

The heats of formation of the hydrogen halides and of water are:

$$H_2 + F_2 \rightarrow 2HF \text{ (gas)} + 2 \times 35.8 \text{ Cal.}$$

(kilocalories)

$$H_2 + Cl_2 \rightarrow 2HCl \text{ (gas)} + 2 \times 22.0 \text{ Cal.}$$

$$H_2 + Br_2 \rightarrow 2HBr \text{ (gas)} + 2 \times 8.6 \text{ Cal.}$$

$$H_2 + I_2 \rightarrow 2HI \text{ (gas)} - 2 \times 6.1 \text{ Cal.}$$

$$H_2 + \tfrac{1}{2}O_2 \rightarrow H_2O \text{ (gas)} + 58.3 \text{ Cal.}$$

From this it may be seen that the heat of formation of the hydrogen halides decreases as the atomic weight of the halogen increases, until hydrogen iodide has a negative heat of formation (endothermic). Heats of formation are frequently useful in predicting the stability of compounds. Those compounds which are formed with the evolution of a large amount of heat are generally the most stable at ordinary temperatures, while those compounds which are formed with the absorption of heat are less stable.

The heats of solution of the hydrogen halides in water are:

$$HF = +11.8 \text{ Cal.}$$

$$HCl = +17.4 \text{ Cal.}$$

$$HBr = +20.0 \text{ Cal.}$$

$$HI = +19.6 \text{ Cal.}$$

The heat of formation and solution of HCl in water, or the heat of formation of HCl in aqueous solution, is the sum of the two quantities: +22.0 Cal. + 17.4 Cal. = +39.4 Cal.

When the following thermochemical data on water are considered, it is seen that the chemical and physical changes involved in the formation and condensation of water are strongly exothermic.

(heat of formation per gram mole) $H_2 + \frac{1}{2}O_2 \rightarrow H_2O$ (gas)	+58.3 Cal.
(− heat of vaporization per gram mole) H_2O (gas) $\xrightarrow{\text{at } 100^\circ \text{ C.}}$ H_2O (liq.)	+ 9.7 Cal.
(− specific heat per gram mole) H_2O (liq. at 100° C.) $\rightarrow$ H_2O (liq. at 16° C.)	+ 1.5 Cal.
then $H_2 + \frac{1}{2}O_2 \rightarrow$ H_2O (liq. at 16° C.)	+69.5 Cal.

This helps to explain why there is so much water present on the earth's surface.

With this brief background, we may now consider examples of the general reaction:

A. $2HX + \frac{1}{2}O_2 \rightarrow H_2O + X_2 \pm$ energy

1. $2HF$ (gas) $+ \frac{1}{2}O_2 \rightarrow$
   2×35.8 Cal.

   H_2O (gas) $+ F_2 - 13.3$ Cal.
   58.3 Cal.

2. $2HCl$ (gas) $+ \frac{1}{2}O_2 \rightarrow$
   2×22 Cal.

   H_2O (gas) $+ Cl_2 + 14.3$ Cal.
   58.3 Cal.

Reaction 1 does not take place because it is endothermic, while reaction 2 takes place because it is exothermic. High temperatures, however, are necessary. The temperature at which this reaction takes place can be reduced by the use of catalytic agents, as in the Deacon process for the commercial manufacture of chlorine. In this process a mixture of air and hydrochloric acid was passed over porous bricks, soaked in a solution of copper sulfate, at about 400° C. Cupric chloride was formed, decomposed into cuprous chloride and free chlorine, the cuprous chloride reoxidized to cupric chloride which again decomposed into cuprous chloride with the liberation of more chlorine, and so on. This process was important because it utilized oxygen of the atmosphere for oxidation and obviated the use of manganese dioxide as in the Weldon process. However, it called for hydrochloric acid made from sodium chloride with sulfuric acid, hence was bound to be superseded by the direct process of making chlorine by electrolysis of sodium chloride wherever electricity could be obtained cheaply.

In aqueous solution, however, the above oxidation of hydrogen chloride does not take place because the heat of formation and solution of HCl is considerably greater than the heat of formation of liquid water as shown by the following thermochemical equation:

$2HCl$ (aq.) $+ \frac{1}{2}O_2 \rightarrow$
2×39.4 Cal.

H_2O (liq.) $+ Cl_2 - 10.4$ Cal.
68.4 Cal.

This reaction is endothermic, hence Hydrochloric Acid and Diluted Hydrochloric Acid of the U.S.P. are stable and differ from hydrobromic acid and Diluted Hydriodic Acid U.S.P. in this respect.

3. $2HBr$ (gas) $+ \frac{1}{2}O_2 \rightarrow$
   2×8.6 Cal.

   H_2O (gas) $+ Br_2 + 41.1$ Cal.
   58.3 Cal.

   $2HBr$ (aq.) $+ \frac{1}{2}O_2 \rightarrow$
   2×28.6 Cal.

   H_2O (liq.) $+ Br_2 + 11.2$ Cal.
   68.4 Cal.

From these reactions may be seen the reason for earlier revisions of the U.S.P. to include a test for free bromine in Diluted Hydrobromic Acid.[8]

4. $2HI$ (gas) $+ \frac{1}{2}O_2 \rightarrow$
   2×-6.1 Cal.

   H_2O (gas) $+ I_2 + 70.5$ Cal.
   58.3 Cal.

The strongly exothermic character of this reaction reveals why hydrogen iodide is so unstable in the presence of oxygen. However, hydrogen iodide is rarely used as such, but is used in aqueous solution, in which the

heat of solution of the hydrogen iodide overcomes in part the heat of formation of the liquid water. Nevertheless, the aqueous product is still very unstable, as shown by the following:

$$2HI\ (aq.) + \tfrac{1}{2}O_2 \rightarrow H_2O\ (liq.) + I_2 + 41.4\ Cal.$$
$$2 \times 13.5\ Cal. \qquad\qquad 68.4\ Cal.$$

This is the reason why a concentrated hydriodic acid is difficult to keep. Bottles in which this acid is stored should be well-sealed, but even under these conditions, a colorless hydriodic acid is almost never seen on the market; it is almost invariably colored, due to the presence of free iodine.[9] In fact, open bottles of this acid frequently have been seen to contain large crystals of iodine that have crystallized out of the aqueous solution because of the oxidizing action of atmospheric oxygen. The U.S.P. Diluted Hydriodic Acid contains a reducing agent [10] and also a precaution that it must not be used if it contains free iodine, while the U.S.P. Hydriodic Acid Syrup also contains a reducing agent in the form of sucrose, which upon hydrolysis yields the reducing sugar, glucose.[11] Despite the presence of reducing agents, however, the U.S.P. directs that tests be made for free iodine in both of these preparations by testing with Starch T.S.

B. $MgCl_2 + \tfrac{1}{2}O_2 \rightarrow MgO + Cl_2$

Since magnesium chloride resulted as a by-product in large quantities in the manufacture of potassium chloride from carnallite (p. 22), this reaction was at one time worked out on a technological scale. When the hydrated magnesium chloride is heated at high temperature, hydrogen chloride as well as chlorine result; this process, therefore, may yield three pharmaceutical products, namely, chlorine, hydrochloric acid and magnesium oxide, and may account for the possible presence, as impurity, of hydrogen chloride in liquid chlorine, of chlorine in Hydrochloric Acid, for which the U.S.P. provides a test,[12] and of chlorides, more specifically "soluble salts," in Magnesium Oxide, for which the U.S.P. provides a test.[13]

C. This method of formation of halogen is also involved in the application of the so-called iodometric methods of pharmaceutical analysis; in these hydrogen iodide, upon reaction with an oxidizing agent, is converted to free iodine, which subsequently is titrated with N/10 sodium thiosulfate. Thus, in the assay of the N.F. Exsiccated Sodium Arsenate, for example, the arsenic acid acts as the oxidizing agent. The reactions involved may be represented as follows: [14]

$$Na_2HASO_4 + 2HCl \rightarrow H_3AsO_4 + 2NaCl$$
$$2KI + 2HCl \rightarrow 2HI + 2KCl$$
$$H_3AsO_4 + 2HI \rightarrow H_3AsO_3 + H_2O + I_2$$

The same reactions are involved in the assay of N.F. Sodium Arsenate Solution and in the assays of U.S.P. Arsphenamine, Neoarsphenamine and certain other organic arsenicals. In the case of these latter medicinals, the organic arsenic is first converted into inorganic arsenate by oxidation with potassium permanganate and hydrogen peroxide.

The U.S.P. XII nitrite assay procedure, as well as both of the nitrite assay methods of the N.F., also involve this method of formation of iodine. In this case, taking Amyl Nitrite U.S.P. XII as an example, the organic ester is hydrolyzed to yield nitrous acid; the latter oxidizes hydrogen iodide to free iodine, which is titrated with N/10 sodium thiosulfate. The reactions involved in this assay may be represented as follows: [15]

$$2C_5H_{11}ONO + 2HOH \xrightarrow{(HCl)} 2C_5H_{11}OH + 2HONO$$

$$2KI + 2HCl \rightarrow 2KCl + 2HI$$
$$2HONO + 2HI \rightarrow 2NO + 2H_2O + I_2$$

This method is also used for the assay of the N.F. Glyceryl Trinitrate Spirit. In the N.F. nitrite assay by the nitrometer method, used in the assay of Ethyl Nitrite Spirit, and in the U.S.P. XIII assay of Amyl Nitrite, the same reactions are involved, except that the volume of the nitric oxide, NO, which is released is measured in a nitrometer.[16]

D. Another example of this method is the oxidation of hydrogen halide by potassium dichromate. This has been used in the past as a substitute for Scheele's method of preparation of chlorine for chlorine water:

$$K_2Cr_2O_7 + 14HCl \rightarrow 2KCl + 2CrCl_3 + 7H_2O + 3Cl_2$$

An analogous reaction, involving the liberation of iodine, is made use of in the U.S.P. method of standardization of Sodium Thiosulfate, Tenth-Normal.[17] Hydrogen iodide, produced by reaction of hydrochloric acid on potassium iodide, is oxidized by a measured amount of N/10 potassium dichromate, and the iodine thus liberated is used to standardize the thiosulfate solution by titration:

$$14KI + 14HCl + K_2Cr_2O_7 \rightarrow 14KCl + 2CrI_3 + 7H_2O + 3I_2$$

$$3I_2 + 6Na_2S_2O_3 \rightarrow 3Na_2S_4O_6 + 6NaI$$

IV. Displacement of Halogen of Higher Atomic Weight in a Halide by Another Halogen of Lower Atomic Weight. The affinity of the halogens toward hydrogen and other electropositive elements or groups decreases with an increase in the atomic weight of the halogen and may be expressed as $F > Cl > Br > I$. On the other hand, the affinity of the halogens toward oxygen and other electronegative elements or groups increases with an increase in the atomic weight of the halogen and may be expressed as $F < Cl < Br < I$. From the first of these two generalizations we may conclude that a halogen of lower atomic weight will displace one of higher atomic weight from its hydrogen compound or metallic salt. These statements also are readily explained by means of thermochemical equations. The reactions involved are employed widely for analytical purposes, hence they are conducted almost invariably in aqueous solution:

$$\underset{2 \times 28.6 \text{ Cal.}}{2HBr\ (aq.)} + Cl_2 \rightarrow \underset{2 \times 39.4 \text{ Cal.}}{2HCl\ (aq.)} + Br_2 + 21.6 \text{ Cal.}$$

$$\underset{2 \times 13.5 \text{ Cal.}}{2HI\ (aq.)} + Cl_2 \rightarrow \underset{2 \times 39.4 \text{ Cal.}}{2HCl\ (aq.)} + I_2 + 51.8 \text{ Cal.}$$

$$\underset{2 \times 13.5 \text{ Cal.}}{2HI\ (aq.)} + Br_2 \rightarrow \underset{2 \times 28.6 \text{ Cal.}}{2HBr\ (aq.)} + I_2 + 30.2 \text{ Cal.}$$

The same thermochemical relationships may be seen to exist for the free halogens and their metallic halides:

$$\underset{2 \times 73.8 \text{ Cal.}}{2KI\ (aq.)} + Cl_2 \rightarrow \underset{2 \times 100.2 \text{ Cal.}}{2KCl\ (aq.)} + I_2 + 52.8 \text{ Cal.}$$

$$\underset{2 \times 89.3 \text{ Cal.}}{2NaBr\ (aq.)} + Cl_2 \rightarrow \underset{2 \times 97.2 \text{ Cal.}}{2NaCl\ (aq.)} + Br_2 + 15.8 \text{ Cal.}$$

$$\underset{2 \times 167.3 \text{ Cal.}}{MgBr_2\ (aq.)} + Cl_2 \rightarrow \underset{2 \times 189.1 \text{ Cal.}}{MgCl_2\ (aq.)} + Br_2 + 43.6 \text{ Cal.}$$

$$\underset{2 \times 73.8 \text{ Cal.}}{2KI\ (aq.)} + Br_2 \rightarrow \underset{2 \times 89.0 \text{ Cal.}}{2KBr\ (aq.)} + I_2 + 30.4 \text{ Cal.}$$

Several examples of this method of formation of bromine and iodine are found in pharmaceutical practice:

A. Chlorine Water, or the U.S.P. Chlorine T.S., is commonly used as a reagent in the

qualitative identification tests for soluble bromides and iodides in both the U.S.P. and the N.F.[18] In employing this test, care should be exercised not to use an excess of Chlorine Water, because excess chlorine will not only liberate iodine from iodides but will also oxidize the iodine to iodic acid, thus rendering the iodine unrecognizable by the usual coloration with Starch T.S. (p. 80).

B. As tests for impurities, these reactions are involved in testing for bromide or iodide in the U.S.P. Hydrochloric Acid, Sodium Chloride, Potassium Chloride and possibly other chlorides and bromides in the U.S.P. and N.F.[19]

C. Iodine is purified by mixing it with potassium iodide and subliming the mixture to remove traces of chlorine and bromine. Any chlorine or bromine present displaces iodine from the potassium iodide and becomes fixed as potassium chloride or potassium bromide, which will not sublime with the iodine.

D. These reactions also find use in the commercial manufacture of bromine from the mother liquids of sea salt and salt wells by electrolysis (p. 24). Another modification is the addition of chlorine to the mother liquids containing metallic bromides, whereby bromine is liberated and is either precipitated as tribromoaniline by the addition of aniline or is absorbed in sodium carbonate solution in the form of sodium bromide and sodium bromate, from which the bromine is recovered in a subsequent operation (p. 31). By these latter methods, bromine is obtained in appreciable commercial quantity from sea water.

E. Assay processes in the U.S.P. and N.F. making use of this method of formation of iodine include those for Chlorinated Lime, Sodium Hypochlorite Solution, Phenol, Resorcinol, Calcium Hypophosphite and others, as well as the standardization of the U.S.P. Bromine, Tenth-Normal (Koppeschaar's Solution). These will be discussed in more detail later.

V. Interaction of Hydrogen Halide with Hydrogen Hypohalite.

$$HX + HOX \rightarrow H_2O + X_2$$

This reaction is primarily of analytical importance, although it is also of significance in other respects, as will be indicated in the examples cited.

A. In the determination of the available chlorine in Chlorinated Lime of the U.S.P. reagents, acetic acid is added to an aqueous mixture of a weighed amount of the sample in water, liberating hydrochloric and hypochlorous acids; these react according to the above general equation to yield chlorine. The chlorine, in turn, liberates iodine from the potassium iodide which has been added and the liberated iodine then is titrated with N/10 sodium thiosulfate; the amount of available chlorine is expressed in terms of the volume of standard sodium thiosulfate required to titrate the liberated iodine. The reactions involved may be represented as follows:[20]

$$Ca\begin{cases} Cl \\ OCl \end{cases} + \begin{matrix} HOOCCH_3 \\ HOOCCH_3 \end{matrix} \rightarrow$$

$$Ca(OOCCH_3)_2 + HCl + HOCl$$

$$HCl + HOCl \rightarrow H_2O + Cl_2$$

$$Cl_2 + 2KI \rightarrow 2KCl + I_2$$

$$I_2 + 2Na_2S_2O_3 \rightarrow 2NaI + Na_2S_4O_6$$

The same reactions are involved in the assay of the U.S.P. Sodium Hypochlorite Solution and the N.F. Diluted Sodium Hypochlorite Solution. In these products, however, the amount of sodium hypochlorite, NaOCl, is determined, and although all of the available chlorine is liberated in the assay process, only half of it is calculated in terms of the active ingredient, NaOCl. Consequently the volumetric factor used in the calculations is different. In this assay the sodium chloride, which is present in the solution from the method of preparation (p. 86), is as important as the sodium hypo-

chlorite, for without the presence of the former, no chlorine would be set free, as is shown in the following reactions:[21]

$$NaCl + NaOCl + 2CH_3COOH \rightarrow 2CH_3COONa + HCl + HOCl$$

$$HCl + HOCl \rightarrow H_2O + Cl_2$$

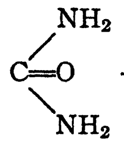
$$Cl_2 + 2KI \rightarrow 2KCl + I_2$$

$$I_2 + 2Na_2S_2O_3 \rightarrow 2NaI + Na_2S_4O_6$$

B. An analogous reaction takes place when Chlorinated Lime is exposed to the atmosphere, the action of CO_2 or carbonic acid of the air forming calcium carbonate with the liberation and loss of chlorine, thus causing the product to deteriorate. For this reason the U.S.P. directs the preservation of the product in airtight containers in a cool dry place;[20] the U.S.P. and N.F. contain similar instructions for preserving all of the hypochlorite preparations.

C. The bleaching and disinfectant actions of Chlorinated Lime, sodium hypochlorite solutions and other hypochlorite yielding preparations, to be discussed later (p. 88), are based in part on this same reaction for the liberation of chlorine.

D. Hydrobromic and hypobromous acids react in an analogous manner to yield water and bromine. These acids can be set free from their salts by the action of another acid or the reaction may be "induced" by other substances, such as urea. The determination of urea in urine by means of the Doremus ureometer * is based on this reaction. It depends upon the oxidation of urea with the liberation of nitrogen, the amount of the latter being directly proportional to the amount of urea present in the urine. The reagents required, which are contained in the N.F. Reagents and Test Solutions,[22] are a strong sodium hydroxide solution and bromine, which react upon mixing to form NaBr and NaOBr (p. 87). The urea induces liberation of bromine from these salts; the bromine reacts with water to liberate oxygen (p. 39), which in turn oxidizes the urea to carbon dioxide, water and nitrogen. The CO_2 is absorbed by the strong alkali, while the nitrogen, being insoluble, rises to the top of the ureometer tube where it is measured volumetrically:



$$+ 1\tfrac{1}{2}O_2 \rightarrow CO_2 + 2H_2O + N_2$$

These exothermic reactions predispose, as it were, the NaBr and NaOBr to react in the presence of urea as though a mineral acid were present, liberating HBr and HOBr, which interact to form Br_2; this in turn liberates the necessary oxygen from the water. The NaOBr might also be regarded as the oxidizing agent, by direct liberation of oxygen.

VI. Interaction of Hydrogen Halide with Hydrogen Halate.

$$5HX + HXO_3 \rightarrow 3H_2O + 3X_2$$

This reaction also is primarily of analytical importance, but is also of significance for other purposes, as will be pointed out in the examples cited.

A. $5HCl + HClO_3 \rightarrow 3H_2O + 3Cl_2$

When hydrochloric acid acts on potassium chlorate, chloric acid is set free and reacts with the excess hydrochloric acid to liberate chlorine. In the past (1860-1910), use was made of this reaction in the preparation of the so-called extemporaneous chlorine water which some druggists found more convenient than the preparation of chlorine water of the U.S.P. according to the method of Scheele. It was the official method of the U.S.P. of 1900 for the preparation of Liquor Chlori Compositus. This reaction also is an explanation of one of the identification tests for the N.F. Potassium Chlorate.[23]

* For a description of this apparatus see catalogue of Sargent or other laboratory equipment house. Directions for urea determination by this method may be found in a laboratory manual on physiologic chemistry.

B. $5HBr + HBrO_3 \rightarrow 3H_2O + 3Br_2$

1. In the standardization of Bromine, Tenth-Normal or Koppeschaar's Solution U.S.P. and in its use in the assay of phenol, resorcinol, calcium hypophosphite and other medicinal chemicals and pharmaceutical preparations containing them, application is made of this reaction. Koppeschaar's Solution contains no free bromine but is a solution of potassium bromide and potassium bromate from which, by the addition of hydrochloric acid, bromine is liberated. In the standardization of this solution, the bromine thus liberated in turn liberates iodine from potassium iodide which has been added, the iodine is titrated quantitatively with N/10 sodium thiosulfate and the normality of the bromine solution calculated from the amount of standard sodium thiosulfate required for titration. The reactions involved may be represented as follows: [24]

$$5KBr + KBrO_3 + 6HCl \rightarrow 6KCl + 5HBr + HBrO_3$$

$$5HBr + HBrO_3 \rightarrow 3H_2O + 3Br_2$$

$$3Br_2 + 6KI \rightarrow 3I_2 + 6KBr$$

$$6Na_2S_2O_3 + 3I_2 \rightarrow 6NaI + 3Na_2S_4O_6$$

2. In the use of Koppeschaar's Solution for the U.S.P. assay of Phenol, the bromine, liberated as in the above reaction from a measured excess of the solution, forms with the phenol a precipitate of tribromophenol. The excess bromine then liberates iodine from potassium iodide, which is added. The iodine is titrated with N/10 sodium thiosulfate, and in this way the amount of excess bromine is determined. This, subtracted from the original amount, gives the amount of bromine required to react with the phenol sample.[25]

3. This same method of formation of bromine finds application in the U.S.P. and N.F. tests for impurity of bromide in bromates, e.g., in Potassium Bromate U.S.P.[26] and of bromate in bromides, e.g., in Ammonium Bromide and Strontium Bromide N.F.[27] Explanation of the possible presence of these impurities is taken up later under the methods of formation and preparation of the bromides and bromates (pp. 56, 80).

4. Commercial application of this reaction in the manufacture of bromine from the mother liquids of sea salt and salt wells has already been mentioned (p. 29). The bromine, liberated from metallic bromides by displacement with chlorine, is removed by a current of air and absorbed in sodium carbonate solution:

$$3Br_2 + 3Na_2CO_3 \rightarrow 5NaBr + NaBrO_3 + 3CO_2$$

The mixture of sodium bromide and sodium bromate thus obtained is acidified with sulfuric acid, liberating free bromine, according to the general reaction; this then is removed by steam and condensed to a liquid. Essentially the same process is used for the extraction of bromine directly from sea water without first removing the sodium chloride by evaporation.

C. $5HI + HIO_3 \rightarrow 3H_2O + 3I_2$

1. Application of this reaction is found in the assay of the U.S.P. Iodine Pentoxide, the N.F. Thymol Iodide and other organic iodine compounds, including the U.S.P. Thyroid, Thyroxin and others. In the assay of Iodine Pentoxide, for example, the iodic anhydride is hydrolyzed to iodic acid, which reacts with hydrogen iodide, formed by action of sulfuric acid on potassium iodide, to liberate iodine; this then is titrated with N/10 sodium thiosulfate. The reactions involved may be represented as follows: [28]

$$I_2O_5 + H_2O \rightarrow 2HIO_3$$

$$10KI + 5H_2SO_4 \rightarrow 10HI + 5K_2SO_4$$

$$10HI + 2HIO_3 \rightarrow 6H_2O + 6I_2$$

$$12Na_2S_2O_3 + 6I_2 \rightarrow 12NaI + 6Na_2S_4O_6$$

In the assay of an organic iodine compound such as Thymol Iodide, the organically combined iodine first is converted into

inorganic iodide by fusing the compound with potassium carbonate. The potassium iodide then is oxidized to potassium iodate by means of potassium permanganate solution. From this point on the procedure is the usual one, with the addition of potassium iodide and dilute sulfuric acid and titration of the liberated iodine with N/10 sodium thiosulfate. The essential reactions involved may be represented as follows:[29]

$$(C_6H_2{-}CH_3{-}C_3H_7{-}OI)_2 + K_2CO_3 + nO_2 \rightarrow 2KI + nCO_2 + nH_2O$$

Thymol Iodide

$$2KI + 4KMnO_4 + 2H_2O \rightarrow 4MnO_2 + 4KOH + 2KIO_3$$

$$10KI + 2KIO_3 + 6H_2SO_4 \rightarrow 10HI + 2HIO_3 + 6K_2SO_4$$

$$10HI + 2HIO_3 \rightarrow 6H_2O + 6I_2$$

$$12Na_2S_2O_3 + 6I_2 \rightarrow 12NaI + 6Na_2S_4O_6$$

2. This method of formation of iodine also is used in the U.S.P. and N.F. tests for impurity of iodide in iodates, e.g., in Potassium Iodate U.S.P. and of iodate in iodides (in Potassium Iodide and Sodium Iodide U.S.P.,[30] and others). Explanation of the possible presence of these impurities will be taken up later under the methods of formation and preparation of the iodides and iodates (pp. 56, 80).

3. Commercial application of this reaction is found in the manufacture of iodine from the concentrated mother liquors of crude Chile saltpeter (p. 22), where the iodine is present largely in the form of sodium iodate. Treatment of these liquors with sodium bisulfite reduces a part of the sodium iodate to sodium iodide; this then reacts with the remainder of the sodium iodate, in the presence of the sodium acid sulfate, to form free iodine:

$$5NaIO_3 + 15NaHSO_3 \rightarrow 5NaI + 15NaHSO_4$$

$$5NaI + NaIO_3 + 6NaHSO_4 \rightarrow 5HI + HIO_3 + 6Na_2SO_4$$

$$5HI + HIO_3 \rightarrow 3H_2O + 3I_2$$

The iodine thus precipitated from solution is removed, washed and further purified by sublimation.

Physical Properties. The most common physical properties of the halogens can best be seen and compared in Table 3.

From this table it may be seen that with an increase in atomic weight of the halogen the state of aggregation changes from gas to liquid to solid, with a corresponding increase in melting point and boiling point. Liquid bromine and solid iodine vaporize below their boiling points; bromine fumes visibly at room temperature, iodine at about 50° C. Bromine at −10° C. exerts considerable vapor pressure, and iodine sublimes at room temperature, crystals forming in the upper part of a partially filled iodine bottle standing on the shelf.*

The solubility of chlorine in alcohol is not recorded because it reacts chemically with this solvent (see methods for preparation of chloral hydrate, chloroform, etc.). Bromine, likewise, is freely soluble in alcohol, but with gradual decomposition. In chloroform, carbon tetrachloride and carbon disulfide, both bromine and iodine are freely soluble. Since these solvents are immiscible with water, they are used to shake out traces of bromine and iodine from aqueous solution. Thus, an amount of iodine scarcely visible in extremely dilute aqueous solution can be concentrated in a few drops of these solvents and be made readily visible to the eye. This property is made use of in the qualitative detection of these halogens when liberated from their halides by chlorine. The characteristic colors imparted to chloroform by the presence of minute quantities of bromine (yellow to orange) and iodine (pink

* The relation of vapor pressure to boiling point, melting point and sublimation should be reviewed in a text on general chemistry.

TABLE 3. PROPERTIES OF THE HALOGENS

NAME	FLUORINE	CHLORINE	BROMINE	IODINE
Symbol	F	Cl	Br	I
Atomic weight	19.00	35.46	79.92	126.92
Physical state	Gas	Gas	Liquid	Solid
Melting point (°C.)	−223	−101.6	−7.3	114
Boiling point (°C.)	−187	−34.6	58.7	184.3
Color of vapor	Light yellow	Greenish-yellow	Reddish-brown	Violet
Specific gravity	1.31 (15° C.)	2.49 (0° C.)	3.12 (15° C.)	4.93 (17° C.)
Solubility in water	Decomposes water	1 in 120 (15° C.)	1 in 30 (20° C.)	1 in 2,950 (20° C.)
Solubility in alcohol	Decomposes alcohol	Reacts chemically	Freely (with reaction)	1 in 13

to violet) makes this a valuable and effective test, either for identification of bromide or iodide as such or as an impurity in other metallic halides.[81] It also is utilized in quantitative work, e.g., the use of chloroform in titrations of iodide with potassium iodate to show the disappearance of iodine when the reaction is complete.[82]

Chemical Properties. The relative affinity of the halogens for hydrogen or other electropositive elements or groups already has been mentioned, and it has been shown how this property is utilized in the liberation of bromine and iodine from their combination with hydrogen and with metals by the action of chlorine (p. 28). On the other hand, because of their relative affinities for oxygen or other electronegative elements or groups, a halogen of higher atomic weight will displace one of lower atomic weight from its oxygen compound or oxy-salt. Thus, iodine will displace chlorine from potassium chlorate:

$$2KClO_3 + I_2 \rightarrow 2KIO_3 + Cl_2$$

Toward hydrogen or other electropositive elements or groups, the halogens exhibit a negative character and a valence of one. Their hydrides of the formula HX are acid in character (p. 44) and the metallic halides or salts are binary compounds (p. 53) in which the halogen has a valence of one. However, they also combine directly with nonmetallic elements, forming such compounds as PI_3, AsI_3, $AsCl_3$, S_2Cl_2, etc., which ordinarily are not regarded as salts. The halogens do not react directly with oxygen or nitrogen.

Toward oxygen or other electronegative elements or groups, the halogens exhibit a positive character and may exert a valence of one, three, five or seven. Here again the hydroxy compounds, the so-called halogen oxy-acids, are acid in character (p. 74), although not as strongly so as the halogen hydrides.

The metallic halides also form double salts, such as $HgI_2 \cdot 2KI$.[83] Such compounds formerly were regarded as molecular addition products, but in the solution of iodine in aqueous potassium iodide, the iodine of the potassium iodide is thought to have changed its valence from one to three or even five and thus manifests the capacity to add two atoms of iodine, viz., $K{-}I\!\begin{smallmatrix} \diagup I \\ \diagdown I \end{smallmatrix}$ or K—I=I=I. Hence, the greater solubility of iodine in aqueous potassium iodide than in water is a manifestation of a chemical

rather than a physical property. The same holds true for chlorine and bromine. In fact, any one of these three halogens is readily soluble in the solution of any water soluble halide, and before the present day Iodine Tincture came into general use, physicians frequently used a solution of iodine in salt water as an antiseptic.*

While the halogens readily combine directly with most elements, metallic as well as nonmetallic, they also react with numerous elements already in other combination. Thus, chlorine reacts with water, especially if the solution is exposed to sunlight; Chlorine Water U.S.P. is unstable (p. 39) because of the reaction:

$$\underset{68.4\ \text{Cal.}}{Cl_2 + H_2O\ (\text{liq.})} \rightarrow \underset{2 \times 39.4\ \text{Cal.}}{2HCl\ (\text{aq.})} + \tfrac{1}{2}O_2 + 10.4\ \text{Cal.}$$

Iodine will react with an analogue of water, hydrogen sulfide, in like manner:

$$\underset{7.2\ \text{Cal.}}{I_2 + H_2S\ (\text{aq.})} \rightarrow \underset{2 \times 13.5\ \text{Cal.}}{2HI\ (\text{aq.})} + S + 19.8\ \text{Cal.}$$

This reaction was made use of at one time in the preparation of Hydriodic Acid Syrup.

The preceding reactions illustrate the reaction of halogens with dihydrides of oxygen and sulfur. Halogens likewise will react with monohydrides, such as sodium hydride, NaH, potassium hydride, silver hydride, etc.:

$$Cl_2 + NaH \rightarrow NaCl + HCl$$

A similar reaction takes place with trihydrides, e.g., NH_3, ammonia, the trihydride of nitrogen, though in part, in this case, hydrogen is not only abstracted but substituted as well, with the formation of such compounds as NI_3.†

As an illustration of the reaction of halogen with a tetrahydride methane, CH_4, may be mentioned. A mixture of methane and chlorine exposed to sunlight is explosive. When controlled, the substitution can take place step by step; hence, by the action of chlorine on natural gas, chloroform and carbon tetrachloride have been obtained.

All of these reactions illustrate the chemical affinity of the halogens for hydrogen. In organic chemistry the reactions are employed extensively for both oxidation and substitution. For example, in the preparation of Chloroform as well as Chloral Hydrate, both reactions take place, i.e., use of chlorine for oxidation of ethyl alcohol to acetaldehyde:

$$Cl_2 + H_2O \rightarrow 2HCl + \tfrac{1}{2}O_2$$

$$CH_3CH_2OH + \tfrac{1}{2}O_2 \rightarrow CH_3CHO + H_2O$$

and use of chlorine for substitution of the acetaldehyde to trichloroacetaldehyde:

$$3Cl_2 + CH_3CHO \rightarrow CCl_3CHO + 3HCl$$

Another illustration of the substitution reaction of halogens with organic compounds may be seen in the use of bromine water as a test for phenol, when the insoluble tribromophenol is formed:

$$3Br_2 + C_6H_5OH \rightarrow C_6H_2Br_3OH + 3HBr$$

The halogens also combine directly with many unsaturated compounds by addition, especially the unsaturated hydrocarbons and their derivatives, to form the corresponding saturated compounds:

$$CH_2{=}CH_2 + Cl_2 \rightarrow CH_2Cl{-}CH_2Cl$$

If, in place of water, the halogens are allowed to act on substituted water, for example metallic hydroxides, not only metallic halides but also hypohalites are formed; this will be discussed under the methods of formation and preparation of these compounds (pp. 56, 86).

Uses. The uses of the halogens are indicated by their properties. Fluorine is extremely active toward most substances; it is

* Strong Iodine Solution, U.S.P. XIII, p. 272, also Iodides Tincture, N.F. VIII, p. 261, are examples of this solubility property.

† For example, see evolution of nitrogen in preparing Decolorized Tincture of Iodine according to the N.F. IV, p. 228.

obtained with difficulty and only with difficulty kept in the free state, hence has found little use as such in the past. However, modern methods of manufacture by electrolysis of anhydrous hydrogen fluoride, solution of the shipping problems created by its great reactivity, plus increasing knowledge of the chemistry of the element and its compounds, give promise of many future applications and uses.[34] Chlorine, bromine and iodine are all of great importance, not only in industry, but also in the medical and pharmaceutical professions.

I. Industrial Uses. Fluorine was marketed in small pressure cylinders for the first time in 1946;[35] its present and possible future uses and applications in industry, as well as its preparation and chemistry, are summarized in the recent publication of a symposium on fluorine held by the American Chemical Society.[36] Among its more commonly known preparations may be mentioned the organic fluorine compounds, especially fluorinated hydrocarbons or fluorocarbons, and their applications in plastics, lubricants and other fields; sulfur hexafluoride, SF_6, as an insulator in high voltage work; Freon, CCl_2F_2, as a refrigerant and in the manufacture of aerosol bombs which came into wide use during World War II for the dispersion of DDT and other insecticides and sodium fluoroacetate, $CH_2F—COONa$, originally known as 1080, as a very toxic substance with wide use as a rodenticide.

Chlorine, prepared electrolytically from sodium chloride, is either compressed into steel cylinders or passed over slaked lime to form bleaching powder; it also is passed into strong caustic soda solution to form a concentrated "bleach" solution (p. 86). Enormous quantities of chlorine in this form are used in bleaching of pulp, paper and cotton and linen fabrics as well as in the production of other chemicals. Important among the latter are the various hypochlorite preparations used for antiseptic and disinfectant purposes (p. 84). Large quantities of liquid chlorine are used in the manufacture of both organic and inorganic industrial and medicinal chemicals, of which potassium chlorate, chloroform, chloral and trichloroacetic acid are only a few examples.

Bromine is used principally in the preparation of hydrobromic acid and of metallic bromides, which are used to a considerable extent in medicine and in photographic work. It also is used in the preparation of a number of organic medicinals and dyestuffs as well as industrial chemicals, of which lead tetraethyl is a notable example.

Iodine is used in the preparation of inorganic iodides and of organic dyes and medicinals, many of the latter, such as iodoform, thymol iodide, etc., being used like iodine itself as antiseptics.

II. Pharmaceutical and Medicinal Uses. The most important forms in which the free halogens are contained in the U.S.P. and N.F. are summarized in Table 4.

Neither fluorine nor any of its compounds is official in the U.S.P. or N.F. and they have no medicinal use as such, although the possible value of fluorine in the prevention of dental caries in the teeth of children has already been referred to (pp. 23, 65).

Chlorine has its greatest medicinal use externally as an antiseptic, germicide and deodorant. In the field of public health and sanitation, chlorine is used routinely in the treatment of the drinking water and swimming pools of municipalities in guarding against the origin and spreading of disease and epidemics. Chlorine Water, when diluted, is used as a gargle in septic sore throat and it has been used internally in weak solution as a gastro-intestinal antiseptic.

As a chemical reagent, chlorine is used for the liberation of bromine and iodine from their halides (p. 28) and also as an oxidizing and chlorinating agent.

Bromine has little use in modern medicine. As a reagent it is employed for the liberation of iodine from iodides and as an oxidizing agent; as a brominating agent it is used for the replacement of hydrogen in

TABLE 4. HALOGENS IN THE U.S.P. AND THE N.F.

NAME	SYNONYM	TYPE OF SOLUTION	STRENGTH
Chlorine Test Solution U.S.P.	Chlorine Water	Aqueous	Saturated
Bromine (Reagent) U.S.P.	....	....	Full strength
Bromine Test Solution U.S.P.	Bromine Water	Aqueous	Saturated
Iodobromide Test Solution U.S.P.	....	Glacial acetic acid	13-14%
Iodine U.S.P.	....	....	Full strength
Iodine (Reagent) U.S.P.	....	....	Full strength
Strong Iodine Solution U.S.P. (with KI)	Lugol's Solution	Aqueous	5%
Iodine Solution N.F. (with NaI)	....	Aqueous	2%
Iodine and Potassium Iodide Test Solution U.S.P.	....	Aqueous	2%
Iodine, Tenth-Normal U.S.P. (with KI)	....	Aqueous	N/10
Gram's Iodine N.F. (with KI)	....	Aqueous	0.33%
Iodine Water N.F.	....	Aqueous	Saturated
Iodine Tincture U.S.P. (with NaI)	....	Hydroalcoholic	2%
Strong Iodine Tincture N.F. (with KI)	....	Hydroalcoholic	7%
Iodine Ampuls N.F. (with NaI)	....	Hydroalcoholic	2%
Iodides Tincture N.F. (with KI and NH_3)	....	Hydroalcoholic	5% (in combination)
Iodine Ointment N.F. (with KI)	....	Fatty and hydrocarbon	4%
Iodized Oil U.S.P.	....	Fatty	40% (in combination)
Stainless Iodized Ointment N.F.	....	Fatty and hydrocarbon	5% (in combination)
Iodine and Zinc Iodide Glycerite N.F.	Diluted Talbot's Solution	Glycerin-aqueous	10%
Phenolated Iodine Solution N.F.	Boulton's Solution	Glycerin-aqueous	(in combination)

organic compounds; it is also used, qualitatively, for detection of the presence and, quantitatively, for the determination of the amount of double bonds in organic compounds, as for example, in the identification test for Ethylene U.S.P.[37] and the use of Iodobromide Test Solution in determining the iodine value of fats and oils.[38]

Much care should be exercised in the use of both chlorine and bromine because of their great volatility and caustic action on the skin and the mucous membranes. When their vapors enter the eye or the respiratory organs, much pain results, and bromine or bromine water in contact with the skin may cause serious burns. As first aid for bromine burns on the skin the spots should be washed well with water, then rubbed with glycerol; later a burn ointment may be applied. Glycerol containing 2 per cent phenol is also effective. A very effective first aid treatment for excessive inhalation of the vapors is to pour 5 or 10 cc. of alcohol into the palm of the hand, rub the hands together to spread it over a larger surface; hold the hands together in cuplike fashion over the nose, inhaling the alcohol vapors deeply and exhaling through the mouth. This treatment is said to be positive and most gratifying in allaying the irritation.

Iodine is employed externally chiefly as an antiseptic in aqueous solutions (with sodium or potassium iodide), in hydro-alcoholic tinctures and in ointments. It is used externally also as a counterirritant. Free iodine is seldom taken internally, although it has been prescribed for goiter in the form of aqueous solution and also in iodized salt. Because of its staining quality on the skin, the hydro-alcoholic tincture has been re-

placed to some extent in practice by the N.F. Iodides Tincture, which is colorless but which is not equivalent in antiseptic action.

As a reagent, iodine is employed in volumetric analysis for the standardization and determination of sodium thiosulfate solutions and for the determination not only of chlorine, bromine and other substances (oxidizing agents) which will liberate iodine from hydriodic acid or potassium iodide, but also for the determination of those substances (reducing agents) which are capable of being oxidized by iodine.* The first of these has already been mentioned (p. 27), and the second will be discussed later (p. 39). As a test solution it is used for the detection of starch, with which it gives a characteristic blue color; it is used as a reagent for some alkaloids and also as a reagent for quantitative determination of double bonds in organic compounds.

Although iodine is less active than chlorine and bromine, cases of iodine poisoning, caused by both internal and external administration, are by no means unknown. The too frequent application of the more concentrated iodine solutions also causes severe burns. The antidote for iodine poisoning is starch, best administered in the form of a thin paste. Demulcents, such as egg white and milk, also are useful, as is a dilute solution of sodium thiosulfate. Iodine stains on the skin or clothing usually can be removed by washing with thiosulfate solution.

HYDRIDES OF THE HALOGENS

History. Although the Arabian alchemists had obtained what we call hydrochloric acid mixed with nitric acid as aqua regia (so-called because it dissolved gold, the king of metals) by dissolving sal ammoniac (ammonium chloride) in aqua fortis (nitric acid) and also by distilling together nitre (potassium nitrate), sal ammoniac and vitriol (sulfuric acid), first mention of the pure acid is found under the name of "Spiritus Salis," prepared from "guten vitriol" and "sal communi," in the writings of the mystic Basilius Valentinus, supposedly compiled in the fifteenth century but in fact compiled about 1600.† "Aqua caustica" and later "Spiritus Salis acidus" were other names given to this acid. Glauber,‡ about 1658, first obtained it by the action of oil of vitriol on common salt ("Spiritus fumans Glauberi") and Stephen Hales,§ about 1727, by the action of oil of vitriol on sal ammoniac. Joseph Priestley,|| who

* Present-day texts on quantitative analysis designate such assays as iodometric assays (iodometry) and iodimetric assays (iodimetry), respectively.

† It is now generally agreed that there never lived a Benedictine monk, Basilius Valentinus, in the fifteenth century who wrote the essays concerned, but that it was about 1600 when someone chose this pseudonym and spread the legend of an earlier knowledge of chemicals and processes which, in fact, had been achieved much later. The most important and original statements of this anonymous author concerned antimony and its compounds.

‡ Johann Rudolf Glauber (1603-1688), a very versatile German chemist, was considered as one of the first and most effective promoters of large scale chemical industry. He is best known to pharmacists for Glauber's salt (Sal Mirabile or sodium sulfate), which, according to physicians of that period, possessed remarkable curative powers.

§ Stephen Hales (1677 or 78-1761) was a prominent English chemist who, besides his activities as a minister, did an amazing amount of scientific research. He developed an apparatus for the collection of gases and also published a work on "Vegetable Statics" which has been regarded as the first book on plant physiology.

|| Joseph Priestley (1733-1804) started his career as a minister in Neetham Market, England, in 1755. Before settling in Birmingham in 1780 he visited Germany, Holland and France, contacting the most important chemists of his time in those countries. Because he was suspected of being an adherent of the ideas of the French Revolution, his home in Birmingham was destroyed and his life threatened by the outraged populace. General opinion turned against him to such an extent that he left England in 1794 for America, where he died ten years later at Northumberland, near Philadelphia. Although, independently of Scheele who preceded him, he discovered oxygen which enabled Lavoisier to overthrow the phlogiston theory, Priestley remained until his death an ardent champion of the theory of phlogiston.

first isolated the gas in 1772 by collecting it over mercury, termed it "marine acid air," while Lavoisier,* believing it to contain oxygen and to be an acid, gave it the name muriatic acid (from the Latin *muria,* brine). By directly combining equal volumes of chlorine and hydrogen, Davy and Gay-Lussac showed that muriatic acid contained no oxygen but was composed entirely of chlorine and hydrogen.

Like hydrogen chloride, hydrogen fluoride was known much earlier than hydrogen bromide or hydrogen iodide. It had been used as early as the seventeenth century for the purpose of etching glass, but it was not until 1771 that Scheele demonstrated this action to be due to an acid. In its aqueous solution it was first prepared by Scopoli, who used silver dishes, the inner walls of which were gilt. Like the other hydrogen halides, hydrogen fluoride was made the object of special study by Gay-Lussac.

In the order of discovery, hydrogen iodide came third, having been discovered in 1813 by Clement and Desormes, who had previously reported Courtois' discovery of iodine (p. 21). The last to be discovered was hydrogen bromide, isolated in 1826 by Balard, who also isolated bromine about the same time.

The role played by the hydrogen halides in modifying and enlarging the views concerning acids held by chemists at the beginning of the nineteenth century has already been alluded to in the historical review of the halogens (p. 20).

* Antoine Laurent Lavoisier (1743-1794), the son of a rich Paris barrister, is best known for his experiments on combustion and for developing the chemistry of oxygen and the overthrow of the phlogiston theory. His oxygen theory of acids, bases and salts laid the foundation for the new chemistry, and, while engaged in controversy over the phlogiston theory for most of his life, he lived to see the fruit of his labors, the antiphlogistic system, emerge victorious and establish itself in France and other countries. Largely because of his service to the government as director of the saltpeter industry and in other positions, he was a victim of the French Revolution and was executed on the guillotine.

The idea of oxygen as an exclusive acid former had to be abandoned, and halogen acids were accepted side by side with oxygen acids until it was ascertained that even in the oxygen acids hydrogen was the characteristic element, the replacement of which by metals gave rise to salts. Therefore, salts were no longer regarded as the products of addition of bases to acids but as condensation products of acids and bases or as metallic substitution products of the acids. The knowledge of the composition of the hydrohalogens made possible one of the most important steps in the advancement of inorganic chemistry.

Occurrence. Because of their acid property, the hydrogen halides are not commonly found in nature. Even if produced as such, they will naturally be neutralized as soon as they come in contact with alkaline soil. An interesting exception to this, however, is the occurrence of hydrogen chloride. It has been found in the exhalations from active volcanoes, especially Vesuvius; in aqueous solution, it has been found in the waters of several of the South American rivers rising in the volcanic districts of the Andes, e.g., in the Rio Vinaigro or Vinegar River. Hydrochloric acid in the free state is also found in the gastric juice of man and other animals. Normally, the gastric juice of humans contains about 0.3 per cent of hydrochloric acid, which is necessary for the process of digestion.

Methods of Formation and Preparation.

I. Direct Union of Halogen with Hydrogen.

$$H_2 + X_2 \rightarrow 2HX$$

A. $H_2 + F_2 \rightarrow 2HF + 2 \times 35.8$ Cal.

This reaction takes places with explosive violence because it is strongly exothermic.

B. $H_2 + Cl_2 \rightarrow 2HCl + 2 \times 22.0$ Cal.

This reaction takes place slowly in diffused daylight but with explosive violence in direct sunlight or magnesium light;

hence, it was called "chlorknall gas" by the Germans. This is the classic experiment of Gay-Lussac, which is used as a lecture experiment in general chemistry to demonstrate the law of combination of gases by volume.

C. $H_2 + Br_2 \rightarrow 2HBr + 2 \times 8.6$ Cal.

This reaction does not take place at lower temperatures even in sunlight; however, the mixture will burn. The temperature of the reaction can be reduced by passing the mixture of the two gases over a platinum catalyst.

D. $H_2 + I_2 \rightarrow 2HI - 2 \times 6.1$ Cal.

This reaction can be made to take place only slowly and incompletely by passing the hydrogen gas and iodine vapors over a heated platinum catalyst.

The above thermochemical equations throw much light on the chemical properties of the hydrogen halides which are discussed later (p. 44).

II. Action of Halogen on Water or Its Analogues.

$$X_2 + H_2O \rightarrow 2HX + \tfrac{1}{2}O_2$$

A. $Cl_2 + H_2O$ (gas) $\rightarrow$
58.3 Cal.

$2HCl$ (gas) $+ \tfrac{1}{2}O_2 - 14.3$ Cal.
2×22 Cal.

This reaction will not take place when the chlorine and water are in the vapor state (compare the reverse of this reaction for the preparation of chlorine, p. 25). However, at the temperature of dissociation of water the reaction will take place, but in this case heat energy has been added to overcome the inherent endothermic nature of the system.

$Cl_2 + H_2O$ (liq.) $\rightarrow$
68.4 Cal.

$2HCl$ (aq.) $+ \tfrac{1}{2}O_2 + 10.4$ Cal.
2×39.4 Cal.

Because of the exothermic nature of this reaction in aqueous solution, Chlorine Water deteriorates. As in the case of the union of hydrogen and chlorine, this reaction is also favored by sunlight, hence Chlorine Water should be kept in small, well-filled, colored bottles and in a cool, dark place. The solution should not be dispensed or used unless it has been prepared recently, and then only in small, well-filled, amber bottles.[39]

B. $Br_2 + H_2O$ (gas) $\rightarrow$
58.3 Cal.

$2HBr$ (gas) $+ \tfrac{1}{2}O_2 - 41.1$ Cal.
2×8.6 Cal.

$Br_2 + H_2O$ (liq.) $\rightarrow$
68.4 Cal.

$2HBr$ (aq.) $+ \tfrac{1}{2}O_2 - 11.2$ Cal.
2×28.6 Cal.

These reactions show that Bromine Water is not apt to deteriorate, hence need not be protected as securely from ordinary diffused light. However, in the presence of sunlight and elevated temperatures, this reaction will occur and Bromine Water will deteriorate, hence the U.S.P. directions for preserving it in a cool place, protected from light.[40]

C. $I_2 + H_2O$ (gas) $\rightarrow$
58.3 Cal.

$2HI$ (gas) $+ \tfrac{1}{2}O_2 - 70.5$ Cal.
2×-6.1 Cal.

$I_2 + H_2O$ (liq.) $\rightarrow$
68.4 Cal.

$2HI$ (aq.) $+ \tfrac{1}{2}O_2 - 41.4$ Cal.
2×13.5 Cal.

These reactions, either in the vapor state or aqueous solution, will not take place (compare the reverse of this reaction for the formation of iodine, p. 26). However, if something is present which will undergo a subsequent exothermic reaction with the oxygen formed above, the reaction of iodine with water may be induced to take place. Such a case is involved in the application of the so-called iodimetric methods of volumetric analysis, where a reducing agent is titrated, either by direct or residual titration, with N/10 iodine solution with the formation of hydrogen iodide and the con-

sequent oxidation of the reducing compound which is being assayed. Thus, in the assay of Exsiccated Sodium Sulfite, U.S.P. Reagents,[41] a weighed amount of the sample is added to a measured excess of N/10 iodine solution, and the excess iodine then is titrated with N/10 sodium thiosulfate. The amount of N/10 iodine required to oxidize the sodium sulfite thus gives a measure of the amount thereof in the sample:

$$\underset{261.7\ \text{Cal.}}{Na_2SO_3\ (aq.)} + \tfrac{1}{2}O_2 \rightarrow \underset{329\ \text{Cal.}}{Na_2SO_4\ (aq.)} + 67.3\ \text{Cal.}$$

The energy evolved by the second reaction of oxygen with sodium sulfite is in excess of that absorbed by the first reaction of iodine with water, so that there is a net energy change on the exothermic side of +25.9 Cal., allowing the first reaction to proceed.

The same reactions for the formation of hydrogen iodide are involved in many other iodimetric assays of U.S.P. and N.F. medicinals, including those of Tartar Emetic, of Arsenic Triiodide, of Arsenic and Mercuric Iodides Solution, of Sulfurous Acid and of others.*

D. $$I_2 + \underset{2.7\ \text{Cal.}}{H_2S\ (gas)} \rightarrow \underset{2\times -6.1\ \text{Cal.}}{2HI\ (gas)} + S - 14.9\ \text{Cal.}$$

$$I_2 + \underset{7.2\ \text{Cal.}}{H_2S\ (aq.)} \rightarrow \underset{2\times 13.5\ \text{Cal.}}{2HI\ (aq.)} + S + 19.8\ \text{Cal.}$$

Although iodine reacts no more readily with liquid water than it does with water vapor, its behavior toward aqueous hydrogen sulfide is very different, as these equations show. Because of the exothermic nature of the latter reaction, an aqueous solution of hydrogen iodide can be prepared by passing a stream of hydrogen sulfide into water in which finely pulverized iodine is suspended. In fact, the U.S.P. of 1880 resorted to this method for preparing Syrup of Hydriodic Acid.[42] The main difficulty, however, was encountered in ridding the resulting solution of excess hydrogen sulfide. If it were stirred or if air were bubbled through it, the hydrogen iodide would be partially reoxidized back to iodine by the action of atmospheric oxygen.

This same reaction also has been used for the commercial manufacture of hydriodic acid solutions. In this case, the precipitate of sulfur is filtered off and the dilute solution of hydriodic acid is concentrated to the desired strength by distilling off the water in the absence of oxygen, i.e., under reduced pressure or in an atmosphere of an indifferent gas such as nitrogen or carbon dioxide.

III. Action of Water (Hydrolysis) on the Halides of Trivalent Elements of Group V. Using $\text{N}\!\!\!\!-$ as a symbol to designate the elements of the nitrogen subgroup of the fifth group of the periodic table, i.e., nitrogen, phosphorus, arsenic, antimony and bismuth, the complete hydrolysis of their halides may be indicated as follows:

$$\text{N}\!\!\!\!-X_3 + 3HOH \rightarrow \text{N}\!\!\!\!-(OH)_3 + 3HX$$

Actually, however, their hydrolysis may occur in steps with the formation of various intermediate and side products, especially with the halides of antimony and bismuth. These and other intermediate and side products in the hydrolysis of antimony and bismuth trihalides will be discussed more fully under their appropriate headings (p. 182).

A. $$PCl_3 + 3H_2O \rightarrow P(OH)_3 + 3HCl$$

This reaction is never used for the preparation of hydrogen chloride because it may be obtained more cheaply and conveniently by other methods. However, the analogous reaction with arsenic triiodide,

$$AsI_3 + 3H_2O \rightarrow As(OH)_3 + 3HI$$

is encountered when the N.F. Arsenic Triiodide is dissolved in water, this compound

* See the assays of these substances in the U.S.P. XIII and N.F. VIII.

being almost completely hydrolyzed in aqueous solution.[43] Likewise, the reaction with the analogue of water, viz., H_2S,

$$2AsCl_3 + 3H_2S \rightarrow As_2S_3 + 6HCl$$

is encountered in the U.S.P. Identification test for arsenites.[44]

B. $PBr_3 + 3H_2O \rightarrow P(OH)_3 + 3HBr$

This reaction is utilized in one of the commercial methods of manufacture of hydrogen bromide and hydrobromic acid. Instead of starting with phosphorus tribromide, it is prepared during the process by allowing liquid bromine to drop on a mixture of red phosphorus, sand and a little water. The liquid phosphorus tribromide, which is formed with some little violence, is easily hydrolyzed to hydrogen bromide and phosphorous acid, and the gaseous hydrogen bromide, evolving from the nonvolatile phosphorous acid after removal of free bromine by passing it over more red phosphorus, is collected in cylinders or absorbed in water to give hydrobromic acid.

C. $PI_3 + 3H_2O \rightarrow P(OH)_3 + 3HI$

This method also is utilized in the commercial manufacture of hydrogen iodide and hydriodic acid, explaining the necessity for the U.S.P. test for phosphorus impurity in its Hydriodic Acid, Reagent.[45] Because of its instability and because of the readiness with which phosphorus triiodide can be obtained by merely mixing amorphous phosphorus and iodine, hydrogen iodide is commonly prepared as needed by merely adding iodine to phosphorus suspended in water. This is the way in which it is frequently prepared extemporaneously when required for reducing purposes in organic chemistry. Methyl iodide, for example, may be prepared by the reaction of methyl alcohol with concentrated hydriodic acid obtained in this way. Methyl iodide, in turn, is a valuable reagent used in the preparation of many synthetic organic medicinals.

IV. Action of a Suitable Acid upon a Metallic Halide.

A. $CaF_2 + H_2SO_4 \rightarrow CaSO_4 + 2HF$

This is the historical method for preparing hydrogen fluoride when used for the purpose of etching glass. The graduation marks on graduates, thermometers, burettes, pipettes, etc., commonly are etched on by means of hydrofluoric acid, either as a gas or in solution (p. 44). The hydrogen fluoride obtained as above may be absorbed in water contained in a paraffin, rubber or plastic flask.

B. 1. $NaCl + H_2SO_4 \rightarrow NaHSO_4 + HCl$

2. $2NaCl + H_2SO_4 \rightarrow Na_2SO_4 + 2HCl$

This is the historical method of preparing the "Spirit of Salt" of Glauber (p. 37) and is still used as a commercial method for the manufacture of hydrogen chloride as a by-product in the manufacture of sodium carbonate (sal soda) according to the LeBlanc process (p. 216). This process,* designed pri-

* The so-called LeBlanc soda process was developed by Nicolas LeBlanc (1743-1806) and the pharmacist Michel J. J. Dizé (1764-1852), although, according to A. Pillars and A. Balland (*Le chimiste Dizé*, Paris, 1906), the credit belongs primarily to Dizé who found the way to make the LeBlanc formula workable. Production on a large scale was started in France in 1791. Before that time, nearly all of the sodium carbonate in France had been obtained from kelp and varec (p. 22), the ashes of sea weeds, supplemented by potash (potassium carbonate), the alkali of land plants, which was imported to western Europe from Russia and America. After the French Revolution, however, there was a demand for sodium carbonate from some source other than sea weeds, and the French government appealed to the chemists of that country to submit processes for the manufacture of soda ash from common salt, a prize of 100,000 francs being offered for the best process. Of the 13 different processes submitted and investigated by the Commission, the one submitted by LeBlanc, an apothecary, and which he had been using in his small factory near Paris, was chosen as the best. His factory became a national establishment soon after 1790, and later other factories were built in France, especially at Marseilles. The industry was established

marily to produce sodium carbonate, was important also for the variety of useful by-products it yielded. As raw materials the process uses sea salt (sodium chloride), sulfuric acid, limestone (calcium carbonate) and charcoal or coal (carbon); it consists essentially of four chemical reactions. First, equimolecular quantities of salt and sulfuric acid are allowed to react, with the evolution of hydrochloric acid:

$$NaCl + H_2SO_4 \rightarrow NaHSO_4 + HCl$$

The HCl thus liberated is quite pure and easy to obtain. The residue of sodium acid sulfate is then heated with more salt, with the liberation of another molecule of HCl which is less pure than that liberated from the first reaction:

$$NaCl + NaHSO_4 \rightarrow Na_2SO_4 + HCl$$

The HCl is absorbed in water as it is given off. In the third step, the sodium sulfate, or "salt cake," formed above is converted into sodium carbonate by mixing it with charcoal or coal and limestone and heating the mixture in a rotary furnace at from 700 to 1,000° C., first forming sodium sulfide:

$$Na_2SO_4 + 4C \rightarrow Na_2S + 4CO$$

which is then converted into sodium carbonate:

$$Na_2S + CaCO_3 \rightarrow Na_2CO_3 + CaS$$

The fourth and final step consists in lixiviating the mixture of calcium sulfide and sodium carbonate, called "black ash," with water, which dissolves the sodium carbonate and leaves the insoluble calcium sulfide.

Not only was this process important for the primary product of soda ash and the chief by-product of hydrochloric acid, but also for the calcium sulfide and the intermediate sodium sulfide. These two products, besides being useful as such, also offered a source of sodium thiosulfate.

in England early in the nineteenth century. Although LeBlanc gave to the world a cheap means of producing the raw material for soap and glass, it is sad to note that he did not benefit from his discovery, but died a pauper in a French asylum.

When this method of preparing hydrogen chloride is used in the laboratory, only reaction 1 above, i.e., equimolecular quantities of salt and sulfuric acid, is utilized because the salt cake, Na_2SO_4, formed in reaction *2* is removed from the reaction flask only with difficulty and with danger of breaking the flask from its expansion and heat of solution when treated with water.

C. $NaBr + H_3PO_4 \rightarrow NaH_2PO_4 + HBr$

In this reaction, the theoretical amount of hydrogen bromide is not obtained because the reaction is reversible. This method has been used to prepare hydrogen bromide in the laboratory. Dilute sulfuric acid also can be used, but concentrated sulfuric acid cannot be used because of the subsequent reaction of the hydrogen bromide and sulfuric acid, resulting in the formation of free bromine and other decomposition products (see below under D).

In commercial practice, as well as in the laboratory, hydrogen bromide has been prepared by the action of orthophosphoric acid on calcium bromide:

$$3CaBr_2 + 2H_3PO_4 \rightarrow Ca_3(PO_4)_2 + 6HBr$$

There is less tendency for the reverse of this reaction to occur because of the insolubility of the tricalcium orthophosphate in water. However, the reverse reaction will take place to a certain extent, resulting in the formation of a soluble acid calcium orthophosphate:

$$Ca_3(PO_4)_2 + 4HBr \rightarrow 2CaBr_2 + Ca(H_2PO_4)_2$$

Hence, a dilute hydrobromic acid thus prepared is likely to contain impurities of calcium bromide and soluble acid calcium phosphate. When calcium bromide and orthophosphoric acid are used in the proportions indicated, it is necessary to carefully control the conditions of temperature and dilu-

tion in order to have the reaction go as far as possible toward completion.

D. $KI + HOOC(CHOH)_2COOH \rightarrow HOOC(CHOH)_2COOK + HI$

By the reaction of potassium iodide and tartaric acid in the above proportions, hydrogen iodide can be obtained satisfactorily, with the formation of potassium acid tartrate, which is sparingly soluble in water. If two moles of KI were used for one of tartaric acid, the yield of HI would theoretically be doubled, but the resulting hydrogen iodide solution would then contain soluble potassium tartrate as an impurity. Thus, by use of the proper proportions of tartaric acid and potassium iodide and by cooling the reaction mixture and using dilute alcohol in place of water for a solvent to still further remove the potassium acid tartrate, a dilute aqueous solution of hydrogen iodide can be prepared, containing only a small amount of impurities. The U.S.P. X made use of this method for the preparation of Diluted Hydriodic Acid, from which Syrup of Hydriodic Acid was prepared.[46]

As in the case of hydrogen bromide, sulfuric acid cannot be used to prepare hydrogen iodide because of the subsequent reaction between the hydrogen iodide and sulfuric acid, with the formation of decomposition products. The sulfuric acid is reduced and, depending on conditions, there is the possibility of sulfurous acid, sulfur dioxide, free sulfur, hydrogen sulfide and free iodine all being present in such a reaction mixture. The reactions occurring may be represented as follows:

$$H_2SO_4 + 2HI \rightarrow H_2SO_3 + I_2 + H_2O$$
$$H_2SO_3 \rightarrow H_2O + SO_2$$
$$SO_2 + 4HI \rightarrow SI_2 + 2H_2O + I_2$$
$$SI_2 + 2HI \rightarrow 2I_2 + H_2S$$
$$SO_2 + 4HI \rightarrow 2H_2O + S + 2I_2$$

The same reactions occur with hydrogen bromide and sulfuric acid, although to a lesser extent since hydrogen bromide is a weaker reducing agent than hydrogen iodide.

V. Action of Halogen (Substitution) on Certain Hydrocarbons. This is a method of formation especially for hydrogen chloride and hydrogen bromide, whenever chlorine or bromine act by substitution (chlorination and bromination) on hydrocarbons; it is widely encountered in organic chemistry.

A. It is used in the laboratory as a method of preparing dry hydrogen chloride gas from naphthalene:

$$C_{10}H_8 + Cl_2 \rightarrow C_{10}H_7Cl + HCl$$
$$C_{10}H_7Cl + Cl_2 \rightarrow C_{10}H_6Cl_2 + HCl$$

B. Hydrogen bromide may be prepared in the same way. In fact, much of the hydrogen bromide of commerce is obtained as a by-product of industrial manufacture of bromobenzene and other brominated hydrocarbons:

$$C_6H_6 + Br_2 \rightarrow C_6H_5Br + HBr$$

VI. Dissociation of Certain Double Halides. This is especially a method of preparation of hydrogen fluoride by heating dry potassium or sodium hydrogen fluoride:

$$KHF_2 \xrightarrow{\Delta} KF + HF$$

Physical Properties. The most common physical properties of the hydrogen halides may be compared in Table 5.

The hydrogen halides are all colorless gases possessing disagreeable, irritating odors. They fume strongly in moist air because their aqueous solutions are less volatile than water, and when mixed with moist air, there is a condensation of the acid to tiny droplets. They are extremely soluble in water, and their aqueous solutions, with the exception of hydrofluoric acid, are strongly acidic.

As will be seen from a study of the several groups of the periodic system, the first member of each group differs more or less in its properties from the other members of that group. Hence, it is not strange to see that

Table 5. Properties of the Hydrogen Halides

Name	Hydrogen Fluoride	Hydrogen Chloride	Hydrogen Bromide	Hydrogen Iodide
Molecular weight	20.00	36.47	80.93	127.93
Physical state	Gas	Gas	Gas	Gas
Boiling point (°C.)	19.4	−85	−67	−35.5
Melting point (°C.)	−93.3	−112.5	−86	−50.8
Specific gravity	0.988 (13.6°)	1.268 (0°)	2.71 (0°)	4.4 (0°)
Solubility in water (Gm. in 100 Gm. H_2O at 20° C.)	35.3	42	49	57
Heat of formation	+35.8 Cal.	+22.0 Cal.	+8.6 Cal.	−6.1 Cal.
Heat of solution	+11.8 Cal.	+17.4 Cal.	+20.0 Cal.	+19.6 Cal.
Specific gravity of sat'd. aq. solution	1.15	1.21	1.49	1.70

hydrogen fluoride stands apart from the other hydrogen halides in its physical properties. This is explained in part by the fact that hydrogen fluoride exists in molecular aggregation under ordinary conditions. With the other three hydrogen halides, however, the regular gradation in physical properties, corresponding to the increase in the atomic weight of the halogen concerned, is strikingly shown in Table 5. It may be pointed out that the same gradation is to be observed among the physical properties of the halogens themselves (p. 32).

The solubility of the hydrogen halides in water is reflected in the specific gravity of the resulting solution, this property being used to determine the strength or concentration of HCl in an aqueous solution of hydrochloric acid and also being one of the U.S.P. descriptions of this and other hydrogen halides.*

Chemical Properties. With the exception of hydrogen fluoride, all of the hydrogen halides are strong acids and give the characteristic reactions of acids. Hydrogen fluoride does not conduct the electric current, does not readily attack metals as do the others and, unlike the other three, it forms acid as well as normal salts, e.g., $NaHF_2$ and NaF. Hydrogen fluoride, unlike the others, acts on silicon dioxide, forming gaseous silicon tetrafluoride:

$$SiO_2 + 4HF \rightarrow SiF_4 + 2H_2O$$

It also attacks glass, a mixture of silicates:

$$Na_2SiO_3 + 6HF \rightarrow 2NaF + SiF_4 + 3H_2O$$

$$CaSiO_3 + 6HF \rightarrow CaF_2 + SiF_4 + 3H_2O$$

This property is involved in the use of hydrogen fluoride for the etching and frosting of glass as well as in dissolving complex silicates in their quantitative assay.

The hydrogen halides react with metals with the formation of the corresponding metallic halide and hydrogen:

$$2M' + 2HX \rightarrow 2M'X + H_2$$

Most of the metallic halides thus formed are water soluble, except those of the heavy metals, as silver, lead, mercury, etc. They likewise react with the metallic hydroxides and metallic oxides with the formation of the corresponding metallic halide and water:

$$M'OH + HX \rightarrow M'X + H_2O$$

$$M'_2O + 2HX \rightarrow 2M'X + H_2O$$

These characteristic reactions are involved in the description and physical properties as well as tests for the identity of numerous

* See Specific Gravity of Hydrochloric Acid, also Diluted Hydrochloric Acid and Diluted Hydriodic Acid U.S.P. XIII, as well as Hydriodic Acid, U.S.P. XIII Reagents.

metals, metallic oxides and hydroxides of the U.S.P. and N.F. They also are involved in the use of a standard solution of hydrochloric acid for the quantitative determination of many of these chemicals.[47]

They react analogously with metallic sulfides with the formation of the metallic halide and hydrogen sulfide:

$$M'_2S + 2HX \rightarrow 2M'X + H_2S$$

This property is utilized not only in the identification of metallic sulfides but also in the production of hydrogen sulfide.[48]

The hydrogen halides also react with metallic carbonates and bicarbonates with the formation of the corresponding metallic halides, carbon dioxide and water:

$$M'_2CO_3 + 2HX \rightarrow 2M'X + CO_2 + H_2O$$
$$M'HCO_3 + HX \rightarrow M'X + CO_2 + H_2O$$

These reactions also are utilized in the identification of the various carbonates and bicarbonates of the U.S.P. and N.F.[49]

The hydrogen halides react characteristically with silver nitrate solution, yielding in each case a precipitate of the corresponding, insoluble silver halide:

$$AgNO_3 + HX \rightarrow AgX + HNO_3$$

The silver halide thus produced may be distinguished by its color and behavior toward ammonium hydroxide. Thus, whereas silver chloride is a white curdy precipitate, soluble in ammonia water, silver bromide forms a yellowish-white precipitate which is difficultly soluble in ammonia, while silver iodide forms a yellow curdy precipitate which is insoluble in ammonia. These properties are used as tests for the identity of the hydrogen halides and also for the identity of the soluble metallic halides.[50] The same reactions are utilized in the gravimetric determination of the hydrogen halides,[51] the soluble metallic halides, soluble silver salts and the gravimetric standardization of silver nitrate solution by drying and weighing the amount of insoluble silver halide produced.[52]

The hydrogen halides react with ammonia and substituted ammonias (amines) by addition to the nitrogen to form the corresponding hydrogen halide of ammonia (ammonium halide) or hydrogen halide of the amine:

$$NH_3 + HX \rightarrow NH_4X$$
$$RNH_2 + HX \rightarrow RNH_3X$$

These reactions are utilized in tests for identity and purity of ammonia and the amines.[53] They are also of importance in the case of the alkaloids in converting the water-insoluble alkaloid into a water-soluble alkaloidal salt, e.g., hydrochloride or hydrobromide.

The hydrogen halides react with double-bond hydrocarbons and their derivatives, adding to the double bond and converting it into the corresponding saturated halogen derivative:

$$R{-}CH{=}CH{-}R' + HX \rightarrow R{-}CH_2{-}CHX{-}R'$$

This reaction is widely encountered in organic chemistry and is utilized, among other purposes, to prepare alkyl halides from the corresponding unsaturated hydrocarbon.

The relative stability of the hydrogen halides toward heat and toward oxidizing agents already has been referred to (p. 25), and it has been seen that, in general, their stability decreases with an increase in the atomic weight of the halogen; thus, hydrogen chloride is oxidized only by drastic means, while hydrogen iodide is very easily oxidized. Conversely, the ability of the hydrogen halides to act as reducing agents increases as the atomic weight of the halogen increases. Thus, whereas hydrogen chloride is not regarded as a reducing agent, hydrogen iodide acts as a powerful reducing agent and is extensively employed for such purpose in both inorganic and organic chemistry.

Uses. Like the halogens, the uses of the hydrogen halides are indicated by their

properties. As already mentioned, hydrogen fluoride is employed chiefly in the etching and frosting of glass and in the chemical analysis of glass and other silicates. It has no medicinal use. The other three hydrogen halides, however, are of importance in pharmacy and medicine as well as in the arts, sciences and industry.

I. Industrial Uses. Hydrochloric acid is found in the technical form as muriatic acid, an impure aqueous solution of varying strength usually comparable to concentrated hydrochloric acid. It is frequently yellow in color because of its content of impurities, especially ferric chloride, chlorine, sulfurous acid, etc.; substances like calcium chloride also have been known to be added to raise its specific gravity, the concentration of the commercial acid being designated by this physical constant. Its greatest industrial uses are in the manufacture of metallic chlorides, the extraction of copper ores and for dissolving metals. Large quantities also are used in the tanning of leather, the dehairing of hides and in lead and tin soldering. It is used widely in the synthesis of other chemicals, both inorganic and organic, such as glue, soap, starch, dyes, etc.

Hydrobromic acid is used in the preparation of metallic bromides, as a solvent for some of the heavy metals and their sulfides and in organic syntheses, especially of dyestuffs.

Hydriodic acid is used chiefly in the synthesis of organic compounds including medicinals, dyes, perfumes and intermediate products.

II. Pharmaceutical and Medicinal Uses. The most important forms in which the hydrogen halides are contained in the U.S.P. and N.F. are summarized in Table 6.

Hydrochloric acid is not used externally, although in dilute solution it has been recommended as a surgical germicide. It has its greatest medicinal use in supplying a lack of this acid in the digestive tract in conditions of digestive upset accompanied by dyspepsia, hypoacidity, achlorhydria, etc. For this purpose it is best dispensed in dilute solution in a pleasant tasting vehicle such as Cherry Syrup N.F. or Compound Pepsin Elixir (Elixir of Lactated Pepsin) N.F. Some authorities say it is beneficial in the treatment of pernicious anemia, a condition usually accompanied by low acid content in the stomach. In sufficiently strong concentration it is irritating and corrosive, especially when taken internally. The best antidote is Milk of Magnesia, sodium bicarbonate or other mild alkali, followed by a mucilaginous demulcent.

As a chemical reagent, hydrochloric acid is used very extensively in the U.S.P. and N.F., and mention has already been made of its use in many tests for identity and purity and, in standard solutions, in the analysis of several U.S.P. and N.F. medicinal chemicals.

Hydrogen bromide does not occur in the present editions of the U.S.P. and N.F. It last occurred in the U.S.P. IX in 10 per cent aqueous solution as Diluted Hydrobromic Acid. Hydrobromic acid is little used medicinally, its action on the system being much like that of the alkali bromides of sodium, potassium, etc., which are much easier to administer. When taken internally in sufficient concentration, it is an irritating and caustic poison, much like hydrochloric acid in this respect. As a chemical reagent, it finds no use in the U.S.P. or N.F.

Hydriodic acid is used medicinally in aqueous solution or in a syrup for the same general therapeutic properties possessed by the alkali iodides, i.e., for its alterative effect in various conditions.

As a chemical reagent, hydrogen iodide seldom is encountered as such in the U.S.P. and N.F., but is widely used for its powerful reducing action. Thus, it is generated from potassium iodide by the action of hydrochloric or sulfuric acids in many iodometric assays (p. 27), where it is utilized in the assay of oxidizing agents.

TABLE 6. HYDROGEN HALIDES IN THE U.S.P. AND THE N.F.

NAME	TYPE OF SOLUTION	STRENGTH
Hydrofluoric Acid U.S.P. (Reagent)	Aqueous	46%
Hydrochloric Acid U.S.P.	Aqueous	35-38%
Hydrochloric Acid U.S.P. (Reagent)	Aqueous	35%
Diluted Hydrochloric Acid U.S.P.	Aqueous	10%
Hydrochloric Acid, Diluted, U.S.P. (Reagent)	Aqueous	10%
Hydrochloric Acid		
Normal, U.S.P.	Aqueous	N/1
Half-Normal, U.S.P.	Aqueous	N/2
Tenth-Normal, U.S.P.	Aqueous	N/10
Fiftieth-Normal, U.S.P.	Aqueous	N/50
Hundredth-Normal, U.S.P.	Aqueous	N/100
Thousandth-Normal, U.S.P.	Aqueous	N/1000
Twentieth-Normal, N.F.	Aqueous	N/20
Nitrohydrochloric Acid N.F. (Aqua Regia)	Aqueous (with HNO_3)	20%
Diluted Nitrohydrochloric Acid N.F.	Aqueous (with HNO_3)	4.4%
Hydriodic Acid U.S.P. (Reagent)	Aqueous	52%
Diluted Hydriodic Acid U.S.P.	Aqueous	10%
Hydriodic Acid Syrup U.S.P.	Syrupy	1.4%

HALIDES OF THE HALOGENS

Several compounds of halogen with halogen are known; although none of them is included in the U.S.P. or the N.F. as such, with the exception of their possible presence in the Iodobromide Test Solution of the U.S.P.,[54] they are quite likely to exist in both bromine and chlorine as impurities or they may be formed in the reactions involving halogens. Since they are of limited pharmaceutical interest, only a brief discussion of these compounds will be given here.

Methods of Formation and Preparation.

I. DIRECT UNION OF THE ELEMENTS.

A. $I_2 + Cl_2 \rightarrow 2ICl$

Iodine monochloride is formed when chlorine gas is passed over iodine until the latter is completely liquefied. Iodine monochloride is a reddish-brown oil which can be crystallized into two different solid modifications by varying the conditions of cooling, i.e., ruby-red needles of the α-form, m.p. 27.2° C. or brownish-red tables of the β-form, m.p. 13.9° C.

B. $I_2 + 3Cl_2 \rightarrow 2ICl_3$

Iodine trichloride is formed in this reaction when iodine is heated gently with an excess of chlorine. The most commonly known modification forms lemon-yellow needles.

Iodine trichloride undergoes dissociation more readily than iodine monochloride. Both are hydrolyzed by water but are soluble in ether and alcohol without apparent decomposition.

Since much of the iodine of commerce is obtained from sources in which it is accompanied by compounds of chlorine, the latter will be formed in all the reactions by which iodine is prepared. Therefore, compounds of chlorine with iodine may be found in iodine as impurity. It is for this reason that it is considered necessary to include a test in the U.S.P. for chlorine as impurity in Iodine,[55] the chlorides of iodine being volatile and subliming with iodine when it is purified by

sublimation unless precautions are taken to remove them (p. 29).

Iodine chloride also may be formed in the test for iodide as impurity in Sodium Chloride unless the directions are followed closely.[56] In this test, any iodide or bromide impurity in the sodium chloride is dissolved out with alcohol. The impurity then is treated with chlorine water which has been diluted with twice its volume of distilled water; the chlorine water is added cautiously, drop by drop. If iodine or bromine are present, they will impart a characteristic color to the chloroform layer. The chlorine of the chlorine water will replace any iodine or bromine in combination, but, the amount of iodine or bromine present being so very small, it is necessary to use much care not to add an excess of chlorine water, otherwise the halogen liberated would combine with the chlorine to form iodine chloride or bromine chloride which might not color the chloroform layer and would pass unnoticed.

C. $I_2 + Br_2 \rightarrow 2IBr$

Just as chlorine may accompany iodine prepared from natural sources, so also may bromine; therefore, compounds of bromine with iodine may be looked for in Iodine.[55] Also, since bromine is prepared from the concentrated mother liquids obtained after crystallizing sodium chloride from sea water, both chlorine and iodine may be expected in bromine. Accordingly, the U.S.P. includes a test for iodine in Bromine and gives a limit for the amount of chlorine present.[57] Whether or not union takes place between bromine and chlorine under such conditions has not been established definitely. Such compounds, if they are formed, are very unstable.

In the U.S.P. tests for iodine chloride or iodine bromide in Iodine [55] these compounds are dissolved in water and filtered from the insoluble iodine. All of the halides then are precipitated by the addition of silver nitrate. Silver chloride and silver bromide are soluble in ammonia water, while silver iodide is not (p. 45); therefore, the next step, dissolving the chloride and bromide of silver in the ammonia water, effects a further separation. The addition of nitric acid to the ammonia solution in the filtrate then precipitates the silver chloride or bromide if any has been formed.

D. $KI + I_2 \rightarrow KI_3$

Another example of the tendency of halogens to combine with each other is found in the compounds of iodine with potassium iodide, with hydriodic acid and with other alkali iodides. Iodine is almost insoluble in water but is quite soluble in solutions of potassium iodide or hydriodic acid (p. 33). Advantage is taken of this property in the preparation of pharmaceutical solutions of iodine, as for example, Strong Iodine Solution (Lugol's Solution), Iodine, Tenth-Normal, U.S.P. and others. Even in hydroalcoholic solutions, such as Iodine Tincture U.S.P. and Strong Iodine Tincture N.F., potassium iodide or sodium iodide is added to make the iodine more soluble and prevent precipitation of iodine when the tincture is dispensed in aqueous vehicles.

The solubility of iodine in aqueous solutions containing potassium iodide usually is explained by assuming that a combination takes place between iodine and potassium iodide, with the formation of a polyhalide of the formula KI_3. In fact, when such a solution is evaporated, dark crystals which agree with the formula KI_3 are obtained. If a solution of iodine, therefore, is to be diluted with a large amount of water, it should contain at least one molecule of potassium iodide for every two atoms of iodine present. This is very nearly the ratio in which these two substances are present in the N.F. Strong Iodine Tincture, and this preparation can be mixed with water in all proportions without precipitating the iodine. With the N.F. VII Stronger Tincture of Iodine (Churchill's Tincture), however,

this is not the case since it does not contain potassium iodide in the ratio of one mole for each two atoms of iodine present; upon dilution of this preparation with water, a precipitate of iodine results.

A solution of hydriodic acid also will dissolve iodine in the same way. When, therefore, a solution of hydriodic acid is decomposed by oxidation (p. 27), the iodine formed is not precipitated but remains in solution, supposedly as HI_3, coloring the solution yellow or brown, until decomposition has proceeded so far that the ratio of iodine to hydrogen iodide has exceeded that required for the formation of HI_3. After this point, crystals of iodine will deposit in the container. Ammonium iodide and other metallic iodides in aqueous solution also will dissolve iodine in the same way.[58]

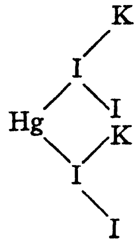
Bromine, like iodine, forms soluble compounds with metallic bromides. Bromine is soluble in water to the extent of about one gram in 30 grams at room temperature. In the N.F. solution used for the estimation of urea, however, 125 grams of bromine are dissolved, with the aid of sodium bromide, in sufficient water to make 1,000 cc. of solution; [59] in this case the solubility of the bromine is increased by the presence of the sodium bromide.

The formation of certain of the so-called complex salts involving metallic halides may also involve the combination of halogen with halogen. For example, Red Mercuric Iodide N.F. is almost insoluble in water but it is soluble in aqueous solutions of iodides, especially potassium iodide.[60] In its preparation from mercuric chloride and potassium iodide by double decomposition, if equimolecular weights of these two chemicals are mixed in aqueous solution, the red mercuric iodide settles out immediately as an insoluble precipitate. If, however, two more moles of potassium iodide are added to the reaction mixture, the red precipitate disappears, going into solution as the soluble complex salt, mercuric potassium iodide:

$$HgCl_2 + 2KI \rightarrow HgI_2 + 2KCl$$

$$HgI_2 + 2KI \rightarrow K_2HgI_4\ (HgI_2 \cdot 2KI)$$

This is the way in which the Mayer's Reagent of the U.S.P., used for the detection of alkaloids, is prepared.[61] The structure of the complex salt thus formed is not known. It might conceivably have such a structure as



in which two atoms of iodine might be linked directly to two other atoms of iodine.

E. Iodine monochloride is formed in certain assay processes involving the reaction of potassium or sodium iodide with potassium iodate in the presence of a sufficient concentration of hydrochloric acid. In the presence of a low concentration of hydrochloric acid, the reaction takes place with the liberation of iodine (p. 31):

$$5KI + KIO_3 + 6HCl \rightarrow 6KCl + 3I_2 + 3H_2O$$

However, in the presence of at least 12 per cent (4N) hydrochloric acid, iodine monochloride is formed according to the following reaction:

$$2KI + KIO_3 + 6HCl \rightarrow 3KCl + 3ICl + 3H_2O$$

It is probable that the above reaction takes place in steps, the iodate being reduced with hydrochloric and hydriodic acids to yield free chlorine and iodine, which then combine to form the iodine chloride:

$$2KI + 2HCl \rightarrow 2HI + 2KCl$$

$$KIO_3 + HCl \rightarrow HIO_3 + KCl$$

$$2HIO_3 + 4HI + 6HCl \rightarrow 6H_2O + 3I_2 + 3Cl_2$$

$$3I_2 + 3Cl_2 \rightarrow 6ICl$$

These reactions are involved in the assays of the U.S.P. Potassium Iodide, Sodium Iodide and the N.F. Red Mercuric Iodide, among others. In the assay of Potassium Iodide, for example,[62] an M/20 solution of potassium iodate is used to titrate the weighed sample in the presence of hydrochloric acid until the purple color of iodine disappears from the chloroform layer.

F. Iodine monochloride is also formed when potassium iodate reacts with free iodine in the presence of at least 12 per cent (4N) hydrochloric acid:

$$KIO_3 + 2I_2 + 6HCl \rightarrow KCl + 5ICl + 3H_2O$$

Here again, this reaction probably takes place in steps, the iodate being reduced with hydrochloric acid to yield free chlorine, which then combines with the iodine to form iodine chloride.

G. Another example of the formation of iodine chloride is found in the assay of the N.F. Arsenic Trioxide Tablets;[63] here the weighed sample is titrated in presence of hydrochloric acid with M/50 potassium iodate according to the following reaction:

$$As_2O_3 + KIO_3 + 2HCl \rightarrow As_2O_5 + ICl + KCl + H_2O$$

THE NONHALOGEN ELEMENTS OF GROUP VII

Of the nonhalogen elements of group VII, manganese, in some of its compounds, is the only one of pharmaceutical importance. Manganese in some form appears to have been known and used by the ancients. For a time it was believed to be an oxide of iron, but Pott, in 1740, showed that pyrolusite contained no iron, and Scheele, in 1774, showed this ore to be the oxide of a new element; finally, in the same year, Gahn isolated the metal itself.

Manganese does not occur in the free state in nature. Its principal ore is pyrolusite, a native form of manganese dioxide (MnO_2), which is widely distributed. Other naturally occurring ores include braunite, Mn_2O_3; manganite, $Mn_2O_3 \cdot H_2O$; hausmannite, Mn_3O_4 and others. The manganese ores usually are found with iron in nature.

Manganese is difficult to prepare in the pure state from any of its oxides by reduction with carbon. A fairly pure sample can be prepared by reduction of the oxide, Mn_3O_4, with aluminum, and a purer form can be attained by electrolysis of its salts, such as manganous chloride. The principal manganese compounds used in the steel industry are alloys with iron, namely, spiegel iron, containing 15 to 25 per cent of Mn, and ferromanganese, containing 70 to 80 per cent. These are made by reducing the mixed iron and manganese ores in a blast furnace.

Manganese metal is gray in color with a reddish tinge. It is brittle, resembling iron, has a specific gravity of 7.2 and melts at around 1,250° C. It tarnishes readily in moist air, with the formation of manganous hydroxide, $Mn(OH)_2$; it combines readily with carbon, sulfur and chlorine, and dissolves in acids with the evolution of hydrogen and formation of the corresponding manganous salts.

The resemblance in chemical properties, so readily apparent among the halogens, is very slight between the halogens and manganese. The only existing analogy is in the formation of a heptoxide, Mn_2O_7, and its hydration product, permanganic acid, which is similar in many respects to the perhalic acids (p. 74). Manganese in its chemistry resembles more closely its horizontal neighbors in the periodic table, viz., chromium and iron. Thus there are many similarities in the properties of the metals themselves; manganic and ferric alums are isomorphous, as are the manganite and chromite salts.

Manganese acts as an electropositive metal, and toward electronegative elements or groups of elements it exhibits valences of plus two, three, four, six and seven. In its divalent state, the manganous ion combines to form such typical compounds as the

hydroxide, halide, sulfide, oxide and salts such as the sulfate, nitrate, carbonate, etc.; it also forms the manganous oxide, MnO.

In its trivalent state, the manganic ion is not so well known, although it forms such compounds as the trihalide and the sesquioxide, Mn_2O_3.

In its tetravalent state, manganese is most commonly known in its dioxide, MnO_2. It also forms manganese tetrahalides, MnX_4, which, however, are unstable and break down to manganous halide and free halogen (p. 24). It also is known in the form of manganites of the formula $M''MnO_3$. The oxide, Mn_3O_4, commonly called manganomanganic oxide, sometimes is considered as a compound of manganous oxide and manganese sesquioxide, $MnO \cdot Mn_2O_3$.

In its hexavalent state, manganese is known chiefly in the manganate ion which forms salts of the formula, M'_2MnO_4, analogous to metallic sulfates, and as the trioxide, MnO_3.

In its heptavalent state it is most familiar as the permanganate, $KMnO_4$, which will be considered later (p. 76).

Manganese is used chiefly in the making of steel, improving the toughness and resistance of steel and adding to its forging and rolling qualities. Manganese dioxide and potassium permanganate, as well as certain manganous salts, viz., Soluble Manganese Citrate, Manganese Glycerophosphate and Manganese Hypophosphite N.F. have some use in medicine.

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4

Metallic Halides

The metallic halides are a group of binary compounds that are composed of metals and halogens in chemical combination. Among them are found several important salts that are essential to the normal functional activities of the body as well as many that are valuable in the treatment or diagnosis of disease. Some of the salts are useful as reagents and as therapeutic aids, while others belong to only one or the other of these categories.

It was observed in the previous chapter that the halogens combine directly with metals to form metallic halides. From the viewpoint of the hydrohalogens, however, the metallic halides are compounds in which the hydrogen has been replaced from one or more molecules of HX by a metal. The halides of the univalent metallic elements have the general or type formula of $M'X$, those of the bivalent metals have the type formula of $M''X_2$, those of the trivalent metals have the type formula of $M'''X_3$, etc.

Occurrence. Of all the naturally occurring metallic halides, sodium chloride is the most abundant. Its importance in the history of the world is significant.[1] Sodium chloride, which is commonly known as salt, is found in all parts of the world. It occurs in salt deposits, in sea water, etc. The compound also is found in the animal body, where it is essential for health. Potassium chloride is found in several salt deposits, among which are the Stassfurt deposits in Germany (p. 22). The salt now is being commercially obtained from the deposits in New Mexico. Potassium chloride is found in the plant kingdom, for example, in Kava Kava, and in the animal kingdom in lesser amounts.

The halides of calcium and magnesium occur naturally, in significant amounts, in the mineral kingdom. Magnesium bromide, for example, occurs in the brines from certain wells and in sea water; these are the sources of the world's bromine supply. Of the other metallic halides, many are found in varying amounts along with other compounds in minerals, rock formations and in mineral waters. They also are found rather widespread in both the plant and animal kingdoms, where they may play important roles in the metabolic processes of living organisms.

Methods of Formation and Preparation. It is not necessary or economically feasible to prepare some of the metallic halides by chemical reactions since they are found abundantly in nature. Sodium chloride, for example, is not manufactured but is only purified to meet the required specifications. Potassium chloride, likewise, occurs in nature and is obtained as such from Sylvite or by the hydrolysis of minerals containing it, such as carnallite (p. 22). These naturally occurring salts may be formed, however, by the same methods by which the other metallic halides are prepared.

The methods of formation and preparation to be considered in this section pertain largely to the simple metallic halides, which can be prepared by general reactions. Specific methods for the preparation of the halides of polyvalent metals will only be emphasized when they fit into the generalized methods that follow.

These general reactions will be encountered very often in the compounding of prescriptions, in the formulating of preparations and other pharmaceutical opera-

tions. A study of these reactions and the general properties of the different groups of metallic halides will make it possible to determine, in advance, the reactions that will take place. Such reactions may be desirable or they may be undesirable.

I. DIRECT COMBINATION OF METAL WITH HALOGEN.

A. $M + X_2 \rightarrow M''X_2$

(M' and M''' halides are also indicated).

It is for this reason that the name halogen (salt former) was given to this group of elements. They yielded salts by direct union with the metal and not by the union of acid and base. This method also applies to the preparation of the halides of nonmetals.

The alkali metals react, very vigorously, with the halogens to form the corresponding alkali halide. It is not feasible, however, to produce them commercially in this manner. A very common method is based upon the reaction of the desired halogen on iron.

$$Fe + X_2 \rightarrow FeX_2$$

and subsequent interaction with the desired alkali carbonate

$$FeX_2 + M'_2CO_3 \rightarrow 2M'X + FeCO_3$$

This method may be involved in the preparation of iodides and bromides in the U.S.P. and N.F., including such compounds as Lithium Bromide and Ammonium Iodide N.F. and Sodium Bromide, Potassium Iodide and Potassium Bromide U.S.P.

The ferrous bromide or iodide is prepared by the reaction of iron wire with bromine or iodine,[2] e.g.,

$$Fe + I_2 \rightarrow FeI_2$$

The ferrous halide then is caused to react with the appropriate carbonate, e.g.,

$$FeI_2 + K_2CO_3 \rightarrow 2KI + FeCO_3$$

B. Compounds of the formula $M''X_2$ commonly are prepared in this manner, as illustrated by the following reactions.

1. $Zn + I_2 \xrightarrow{\Delta} ZnI_2$

This reaction is brought about by heating a mixture of zinc and iodine in water on a water bath.

2. $Hg + Cl_2 \rightarrow HgCl_2$

The mercury is heated nearly to boiling, and chlorine is mixed with it. The salt sublimes as it is formed.

3. $Hg + I_2 \rightarrow HgI_2$

This reaction will take place when mercury and iodine are triturated intimately in a mortar.

4. $Pb + Cl_2 \rightarrow PbCl_2$

If any $PbCl_4$ is formed by the oxidizing action of chlorine on lead, it readily dissociates into $PbCl_2$ and Cl_2.

C. The halides of certain metals of the third and fifth groups, as well as iron of group VIII, may be prepared by direct union, as illustrated in the following reactions. Aluminum Chloride N.F., Arsenic Iodide N.F., and Ferric Chloride U.S.P. are official representatives.

1. $2Al + 3Cl_2 \rightarrow 2AlCl_3$

This reaction takes place when chlorine is passed over heated aluminum.

2. $2As + 3I_2 \rightarrow 2AsI_3$

The arsenic and iodine are fused together and heated to a temperature of about 110° C. to purify the product by sublimation.

3. $2Fe + 3Cl_2 \rightarrow 2FeCl_3$

Ferric chloride is formed when heated iron reacts with chlorine.

4. $2Bi + 3I_2 \rightarrow 2BiI_3$

Bismuth and iodine will react in this manner when fused together with the aid of heat.

II. Action of Hydrohalogen upon Metals.

A. $2M + 2HX \rightarrow 2M'X + H_2$

$2Na + 2HCl \rightarrow 2NaCl + H_2$

This reaction takes place with violence in connection with the alkali metals. The heavy metals in group I, namely, copper, silver and gold, react only very slightly or not at all since they are below hydrogen in the activity series.

B. $M + 2HX \rightarrow M''X_2 + H_2$

1. $Zn + 2HCl \rightarrow ZnCl_2 + H_2$

This reaction was involved in the test for identity of zinc in the U.S.P. IX and also in the preparation of Solution Zinc Chloride in the same revision.[3] Zinc Chloride N.F.[4] also may be prepared by this reaction.

2. $Fe + 2HCl \rightarrow FeCl_2 + H_2$

This is the first reaction in the preparation of Ferric Chloride Solution N.F. when prepared by the usual methods.[5] Iron acts as member of group two in this reaction.

3. $Sn + 2HCl \rightarrow SnCl_2 + H_2$

Tin, in its lowest valence, acts as a member of the second group just as iron, in its lowest valence, does in the preceding example. Stannous Chloride U.S.P. (Reagent) may be prepared in this manner.

As with the heavy metals of group I, the heavy metals of group II react much less readily with the hydrohalogen acids, mercury being inactive toward concentrated hydrochloric acid.

III. Action of Hydrohalogen upon Metallic Hydroxides, Oxides, Sulfides, Carbonates, Etc.

A. $M'OH + HX \rightarrow M'X + H_2O$

This reaction is of common and frequent occurrence in the U.S.P. and the N.F. It is involved in the assay of some of the hydrohalogen acids and the metallic hydroxides of the U.S.P. and N.F. Such reactions are known as neutralization.

1. $NaOH + HCl \rightarrow NaCl + H_2O$[6]
2. $KOH + HCl \rightarrow KCl + H_2O$[7]
3. $NH_4OH + HCl \rightarrow NH_4Cl + H_2O$
4. $NH_4OH + HBr \rightarrow NH_4Br + H_2O$
5. $NH_4OH + HI \rightarrow NH_4I + H_2O$

The latter three reactions may be utilized in the methods of preparation of Ammonium Chloride U.S.P. and of Ammonium Bromide and Ammonium Iodide N.F. by neutralizing ammonia or ammonia water with the appropriate hydrohalogen and evaporating the resulting solution.

2. $M''(OH)_2 + 2HX \rightarrow M''X_2 + 2H_2O$

$Ba(OH)_2 + 2HCl \rightarrow BaCl_2 + 2H_2O$[8]

$Ca(OH)_2 + 2HCl \rightarrow CaCl_2 + 2H_2O$

When Lime Water (Calcium Hydroxide Solution) is taken internally, the hydrochloric acid in the stomach is neutralized, as shown in this reaction.

3. $M'''(OH)_3 + 3HX \rightarrow M'''X_3 + 3H_2O$

$Bi(OH)_3 + 3HCl \rightarrow BiCl_3 + 3H_2O$[9]

$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$[10]

These two reactions explain, in part, the action of Bismuth Magma and of Aluminum Hydroxide Gel, respectively, when used as antacids. The reaction is rather slow and thus may offer protection against hyperacidity for several hours. This is an advantage over compounds such as $Ca(OH)_2$.

B. 1. $M'_2O + 2HX \rightarrow 2M'X + HOH$

No examples of this reaction are found in the U.S.P. or N.F.

2. $M''O + 2HX \rightarrow M''X_2 + H_2O$

$CaO + 2HCl \rightarrow CaCl_2 + H_2O$

This reaction is among the N.F. tests for Lime.[11]

$$HgO + 2HCl \rightarrow HgCl_2 + H_2O$$

This example is found in the tests for identification of Yellow Mercuric Oxide U.S.P. and Red Mercuric Oxide N.F.[12] It

is also a method for the preparation of Mercuric Chloride N.F.

3. $M'''_2O_3 + 6HX \rightarrow 2M'''X_3 + 3H_2O$

$$As_2O_3 + 6HCl \rightarrow 2AsCl_3 + 3H_2O$$

The importance of this reaction is illustrated by the test for solubility of Arsenic Trioxide U.S.P.[13] It is also of importance in the preparation of Arsenious Acid Solution N.F.;[14] the arsenic trichloride, however, is partially hydrolyzed (p. 182).

C. 1. $M'_2S + 2HX \rightarrow 2M'X + H_2S$

When Sulfurated Potash N.F. is treated with hydrochloric acid, the above reaction occurs (p. 127).

2. $M''S + 2HX \rightarrow M''X_2 + H_2S$

$$FeS + 2HCl \rightarrow FeCl_2 + H_2S$$

This reaction is important in the tests for Ferrous Sulfide U.S.P.[15] and in the preparation of Hydrogen Sulfide U.S.P.

D. $M'_2CO_3 + 2HX \rightarrow 2M'X + H_2O + CO_2$

This reaction occurs whenever a metallic carbonate or bicarbonate is treated with a hydrohalogen. It is one of the common tests for the identification of carbonates and bicarbonates.

$$(NH_4)_2CO_3 + 2HI \rightarrow 2NH_4I + H_2O + CO_2$$

One of the methods for the preparation of Ammonium Iodide N.F. is the neutralization of ammonium carbonate with hydriodic acid and the evaporation of the resulting solution. An analogous reaction may be used for the preparation of Ammonium Bromide N.F. The reaction between Ammonium Carbonate U.S.P. and an acid is shown in the generalized form.

2. $M''CO_3 + 2HX \rightarrow M''X_2 + H_2O + CO_2$

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

This reaction takes place when Precipitated Calcium Carbonate U.S.P. is given internally as an antacid. It is also described in the U.S.P. test for acid-insoluble substances in Precipitated Calcium Carbonate.[16]

$$CaCO_3 + 2HBr \rightarrow CaBr_2 + H_2O + CO_2$$

$$SrCO_3 + 2HBr \rightarrow SrBr_2 + H_2O + CO_2$$

The three reactions above may be utilized as methods for the preparation of the corresponding metallic halides, i.e., Calcium Chloride U.S.P., Calcium Bromide N.F. and Strontium Bromide N.F.

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

$$BaCO_3 + 2HCl \rightarrow BaCl_2 + H_2O + CO_2$$

$$FeCO_3 + 2HCl \rightarrow FeCl_2 + H_2O + CO_2$$

$$MgCO_3 + 2HCl \rightarrow MgCl_2 + H_2O + CO_2$$

These reactions are involved in the solubility tests under the corresponding metallic carbonates of the U.S.P. and the N.F. (Magnesium Carbonate U.S.P. is a hydrated carbonate, and this reaction is only partially complete.)

IV. Action of Halogen upon Metallic Hydroxide. This method involves three different steps. At room temperature, when halogen is allowed to react with metallic halide, the following reaction takes place:

A. $$\begin{array}{lcccl} M'\boxed{OH} & X & & M'X & \\ & + & \rightarrow & & + H_2O \\ M'O\boxed{H} & X & & M'OX & \end{array}$$

For every molecule of metallic halide, one of metallic hypohalite is also formed. For the purpose of the manufacture of metallic hypohalites, the temperature is kept low, whereas for the manufacture of metallic halides, the reaction mixture is heated and the second step occurs:

$$3M'OX \xrightarrow{\Delta} 2M'X + M'O_3X$$

Thus, for every molecule of metallic halate formed, five molecules of metallic halide are produced. For the production of pure metal-

lic halide, the halate is heated with carbon, the third step, whereby it is reduced to halide:

$$M'O_3X + 3C \xrightarrow{\Delta} M'X + 3CO$$

This reaction completes the conversion of all the halogen employed in the original reaction into metallic halide.

This method may be used commercially for the preparation of Sodium Bromide, Sodium Iodide, Potassium Bromide and Potassium Iodide, official halides of the U.S.P.* These reactions account for the possible presence of a halate as an impurity in these halides and the necessity for the U.S.P. tests.†

$$\begin{array}{lcccl} \text{1. Na}\boxed{\text{O H}} & & \text{Br} & \text{NaBr} & \\ & + & \rightarrow & & + H_2O \\ \text{Na O}\boxed{\text{H}} & & \text{Br} & \text{NaOBr} & \end{array}$$

In the preparation of the alkaline hypobromite solution for the estimation of urea in urine by the Doremus method (p. 30), the bromine solution is added to an aqueous solution of sodium hydroxide. The reaction results in the formation of a solution of sodium bromide and sodium hypobromite.

$$\begin{array}{lcccl} \text{2. } NH_4\boxed{\text{O H}} & & \text{I} & NH_4I & \\ & + & \rightarrow & & + H_2O \\ NH_4\text{ O}\boxed{\text{H}} & & \text{I} & NH_4OI & \end{array}$$

* See commercial methods of preparation for these four metallic halides. In the commercial process, free halogen is added to an aqueous solution of the caustic alkali until the alkali solution no longer decolorizes it. The resulting solution then is evaporated to dryness, yielding a residue of the halide and halate. This residue then is mixed with carbon in the form of wood charcoal, and the mixture is heated to a red heat in a metallic container, during which time the metallic halate is reduced, producing only the halide. The mixture then is cooled, lixiviated with water and the metallic halide obtained upon evaporation of the aqueous filtrate.

† If the metallic halate is not completely reduced to halide, it will be present as an impurity. See, for example, the U.S.P. XIII test for iodate impurity in Potassium Iodide, p. 427. For the explanation of this test see page 135.

When the Strong Ammonia Solution is added to the iodine-potassium iodide solution in the preparation of Iodides Tincture N.F.,[17] a similar reaction presumably takes place, resulting in the formation of the analogous ammonium compounds.

$$\begin{array}{lcccl} & \diagup\boxed{\text{O H}} & \text{X} & & \diagup X \\ \text{B. } M'' & + & & \rightarrow M'' & & + H_2O \\ & \diagdown\text{ O}\boxed{\text{H}} & \text{X} & & \diagdown OX \end{array}$$

With the hydroxides of divalent metals, the above reactions must be modified, hence a mixed salt, a metallic halide-hypohalite results.

$$\begin{array}{lcccl} & \diagup\boxed{\text{O H}} & \text{Cl} & & \diagup Cl \\ \text{1. Ca} & + & & \rightarrow \text{Ca} & & + H_2O \\ & \diagdown\text{ O}\boxed{\text{H}} & \text{Cl} & & \diagdown OCl \end{array}$$

The action of chlorine on slaked lime, in the preparation of Chlorinated Lime U.S.P.[18] results in the formation of a calcium chloride-hypochlorite (p. 87).

V. Double-displacement Reactions Between Metallic Halides and Other Suitable Salts.

A. $M'X + M'\text{ (salt)} \rightarrow M'X + M'\text{ (salt)}$

1. $NaCl + AgNO_3 \rightarrow AgCl + NaNO_3$

2. $KI + HgNO_3 \rightarrow HgI + KNO_3$ ‡

3. $2NaCl + Hg_2SO_4 \rightarrow 2HgCl + Na_2SO_4$

In these reactions, AgCl, HgI (Yellow Mercurous Iodide N.F.) and Mild Mercurous Chloride N.F. are obtained as insoluble precipitates. The reaction between silver nitrate and sodium chloride is the basis for the assay of sodium chloride and many of its preparations, as well as for qualitative tests.

‡ When potassium iodide is in excess of the mercurous nitrate, a black precipitate of metallic mercury is obtained. For this reason, the KI solution is always added to the mercurous nitrate solution with constant agitation.

4. $NaCl + NH_4HCO_3 \rightarrow$

$$NH_4Cl + NaHCO_3$$

This reaction is encountered in the Solvay process for the manufacture of sodium bicarbonate and sodium carbonate. The ammonium chloride is more soluble than the sodium bicarbonate and separation can be effected by this property.

5. $2KBr + (NH_4)_2SO_4 \rightarrow$

$$2NH_4Br + K_2SO_4$$

6. $2KI + (NH_4)_2SO_4 \rightarrow$

$$2NH_4I + K_2SO_4$$

Ammonium Bromide N.F. and Ammonium Iodide N.F. may be prepared by these reactions. The solubility of ammonium bromide is 1 Gm. in 1.3 cc. of water, and that of ammonium iodide is 1 Gm. in 0.6 cc. of water, while 1 Gm. of potassium sulfate is soluble in 10 cc. of water.

7. $2KI + HgCl_2 \rightarrow HgI_2 + 2KCl$

The Red Mercuric Iodide N.F. separates when aqueous solutions of Potassium Iodide and Mercuric Chloride are mixed simultaneously, in equivalent amounts. When Potassium Iodide is in excess, a water-soluble complex salt is formed.[19]

8. $2NaCl + HgSO_4 \xrightarrow{MnO_2}$

$$HgCl_2 + Na_2SO_4$$

The mercuric chloride is separated from the reaction mixture by sublimation. The manganese dioxide prevents the reduction to the mercurous salt.

9. $FeCl_3 + 3CH_3COONH_4 \rightarrow$

$$Fe(CH_3COO)_3 + 3NH_4Cl$$

The N.F. formula for Iron and Ammonium Acetate Solution[20] involves the mixture of ferric chloride and ammonium acetate.

VI. Heating a Metallic Halate or Perhalate.

$$4M'O_3X \xrightarrow{\Delta} 3M'O_4X + M'X$$

$$3M'O_4X \xrightarrow{\Delta} 3M'X + 6O_2$$

$$4KO_3Cl \xrightarrow{\Delta} 3KO_4Cl + KCl$$

$$3KO_4Cl \xrightarrow{\Delta} 3KCl + 6O_2$$

These reactions are used in the N.F. test for the identity of Potassium Chlorate.[21] They are also employed as a method for the preparation of oxygen (p. 93).

Properties and Uses.

I. Halides of the Formula M'X. The M'X compounds are the halides of the elements of group I of the periodic table. This group of metals commonly is divided into the alkali metals and the heavy metals (p. 250). The ammonium ion is included with the alkali metals when discussing their compounds, and the mercurous salts are grouped with the salts of the heavy metals, due to their respective analogous properties.

The metallic halides are solids, in contrast to the halides of the nonmetals, which are usually liquids or gases. The volatility of the metallic halides increases with an increase in the atomic weight of the halogen. The volatility and partial decomposition of these salts at higher temperatures is made use of in the flame tests for the respective metallic component: lithium halides impart a crimson color to a nonluminous flame, sodium halides give a yellow color and potassium halides produce a violet color under the same conditions. The melting points decrease with an increase in the atomic weight of the halogen. Thus sodium fluoride melts at 992° C., sodium chloride at 804° C., sodium bromide at 768° C. and sodium iodide at 651° C.

Anhydrous alkali halides crystallize as cubes. They may also crystallize as monoclinic prisms with water of hydration, such as $NaBr \cdot 2H_2O$, when allowed to form under favorable conditions. These similarities are not always observed since these halides are frequently purchased and used in a granular or powder form.

The metallic halides of the alkali metals and the ammonium halides are readily solu-

ble in water, forming neutral solutions. Lithium and sodium fluorides are notable exceptions in that they are much less soluble than the other halides. The solubility increases, in general, with an increase in the atomic weight of the halogens; thus, the iodides are more soluble than the bromides and the bromides more soluble than the chlorides. The halides of cesium are exceptions in that they are decreasingly soluble with the increase in molecular weights.

Alkali chlorides, with the important exceptions of the sodium and potassium salts, are soluble in alcohol. The analogous bromides and iodides are generally soluble in this solvent. The M′X compounds are also soluble in glycerin but are insoluble in ether, chloroform and similar solvents.

The halides of the heavy metals of group I and mercurous mercury are insoluble in water and in the other common solvents. This property is used to detect the presence of all soluble halides by an interionic reaction between the silver ion, for example, since it is the one most commonly used, and the halide ion according to the reaction:

$$X^- + Ag^+ \rightarrow AgX$$

The differences in color as well as their solubilities in different reagents, such as Ammonia T.S., are used to differentiate between the chloride, bromide and iodide ions. Silver fluoride is more soluble than the other silver halides. It is interesting to observe that aurous chloride is changed in warm water solution to auric chloride and gold. The formation of the insoluble silver, mercurous mercury and other halides results in important incompatibilities which the pharmacist must anticipate. Soluble silver salts, for example, frequently are prescribed; any soluble chloride, when added to such solutions, would give undesirable reactions since the silver ions would be removed.

Sodium Chloride U.S.P. is available as a white crystalline powder or as colorless hexahedral crystals; after drying at 110° C. for two hours it contains not less than 99.5 per cent of NaCl. The hygroscopic property of Sodium Chloride is due to traces of magnesium chloride or calcium chloride that are not removed in the purification process. The N.F. describes Sodium Chloride Tablets, the usual sizes being 5, 7½, 10 and 15 grains each. There are several aqueous preparations that also contain this salt.

Sodium chloride is present in all parts of the body. The body requirements are normally filled by the salt that is used as a condiment in foods. When working or exercising in hot climates or in other situations which result in a loss of sodium chloride due to perspiration, it may be necessary to take additional amounts to maintain the proper balance. Sodium Chloride Tablets are commonly used for this purpose; however, a 0.1 to 0.2 per cent solution may be used instead.

Sodium chloride is important for the preparation of isotonic solutions. A very delicate balance exists between the fluids and tissues in the body. When a solution of a chemical is introduced by hypodermic injection into a tissue or intravenously, it is essential that such solutions have the same osmotic pressure as the fluids that are already present. Such solutions are said to be "isotonic." Solutions that are more concentrated are said to be "hypertonic"; when used, they cause a dehydration of the surrounding tissues by causing the water to flow out of the cells. A solution of less concentration than that required to produce isotonicity is said to be "hypotonic"; an injection or application of such solutions induces a flow of water into the cells, which may result in bursting them. Isotonic Sodium Chloride Solution U.S.P. contains not less than 0.85 per cent and not more than 0.95 per cent, or an average of 900 mg. of NaCl per 100 cc. This solution is known as Physiological Salt Solution and as Normal Saline Solution. It is prepared by dissolving 900 mg. of Sodium Chloride U.S.P. in enough distilled water to make 100 cc. and filtering until clear. If the solution is for

TABLE 7. METALLIC CHLORIDES (M′Cl) OF PHARMACEUTICAL IMPORTANCE

Formula	Chemical Name	Common Names	Solubility (Gm. per cc. at 25° C.)		Characteristics Affecting Storage Requirements
			In Water	In Alcohol	
Alkali Metals and Ammonium Salts					
NaCl	Sodium Chloride	Salt	1-2.7	Insoluble	Hygroscopic
KCl	Potassium Chloride	....	1-2.8	Insoluble	Stable
LiCl	Lithium Chloride	....	1-1.25	Soluble	Deliquescent
NH_4Cl	Ammonium Chloride	Sal Ammoniac Muriate of Ammonia	1-2.6	1-100	Stable
Heavy Metals					
AgCl	Silver Chloride	....	Insoluble	Insoluble	Blackens on exposure to light
HgCl	Mercurous Chloride	Calomel "Mild Mercurous Chloride"	Insoluble	Insoluble	Darkens on exposure to light

parenteral use, it is necessary to sterilize it according to specific directions given in the U.S.P. It is important to note that bacteriostatic substances may not be added to Isotonic Sodium Chloride Solution or any of its accepted nonmedicated modifications.

When Isotonic Sodium Chloride Solution is used in the living body, the organism can readily establish a balance between the ions in solutions. Excised tissue cannot accomplish this readjustment, so that a balanced solution was required to meet this condition. Ringer's Solution U.S.P., which is also known as Isotonic Solution of Three Chlorides, is a solution containing Sodium Chloride, Potassium Chloride and Calcium Chloride in such concentrations that an isotonic solution is produced. The solution is prepared by using only 8.6 Gm. of Sodium Chloride (instead of the 9 Gm. per 1,000 cc. of solution in the Normal Saline Solution). The addition of 0.3 Gm. of Potassium Chloride and 0.33 Gm. of Calcium Chloride for each 1,000 cc. of the solution is the *equivalent* of the 0.4 Gm. of Sodium Chloride which would be required to make it isotonic. Practically all compounds that may be used in collyria or for parenteral use have an equivalent; when the amount of this substance is specified, its sodium chloride equivalent can be calculated from known data or factors [22] that have been determined, and then a sufficient quantity of Sodium Chloride is added to make the finished solution isotonic. Such solutions also may be buffered to obtain a certain pH range, and the buffering salts must also be taken into consideration for their effects upon isotonicity.

Potassium Chloride U.S.P. contains not less than 99 per cent of KCl after it has been dried at 110° C. for two hours, and in the drying process, the loss in weight must not exceed 1 per cent. The salt is stable in air and is commonly found as cubical crystals or as a white granular powder. Potas-

sium Chloride Tablets, which usually contain 300 or 500 mg. of the salt, also are described in the U.S.P.

Potassium Chloride is used as a diuretic, and more recently it has been used for its effect in alleviating the symptoms of certain allergies.[28] Its use in Ringer's Solution was referred to under Sodium Chloride.

Lithium Chloride is not used pharmaceutically or medicinally. It is produced in the stomach and in the test tube when Lithium Carbonate N.F. comes into contact with hydrochloric acid.

Ammonium Chloride U.S.P. contains not less than 99.5 per cent of NH_4Cl, after being dried over sulfuric acid for four hours. In this drying process, the loss in weight must not exceed 0.5 per cent. The principal chemical reactions are those of ammonium ions and chloride ions. Thus, it will give off ammonia from a warm alkaline solution and will form insoluble precipitates with soluble silver, mercurous mercury or lead salts. Aqueous solutions of ammonium chloride are neutral when freshly prepared, but they quickly develop a pH of 4.6 because of hydrolysis.

Ammonium Chloride is described as a white, crystalline powder. The U.S.P. also describes Ammonium Chloride Capsules, which usually contain 300 mg. or 500 mg. of the salt, and the N.F. describes Ammonium Chloride Tablets containing the same amount. The most characteristic action of this salt is to increase the flow of secretions; it is used widely as an expectorant, especially in cough syrups. In larger doses, it acts as a diuretic.

Silver Chloride is best known as a practically water-insoluble, curdy, white precipitate that is produced when Silver Nitrate T.S. is added to solutions containing chloride ions. Its property of turning black upon exposure to light, due to the reduction of the silver ion to metallic silver, is used to further establish the presence of a chloride. Silver chloride is soluble in ammonium hydroxide, forming the silver ammonia ion $[Ag(NH_3)_2]^+$, in an aqueous solution of a soluble cyanide forming the silver cyanide complex ion $Ag(CN)_2^-$ and in an aqueous solution of sodium thiosulfate forming the $[Ag_2(S_2O_3)_3]^{4-}$ ion.

Silver chloride is official only as Colloidal Silver Chloride, which is known as Lunosol N.N.R. This preparation contains from 9 to 11 per cent of AgCl which has been rendered colloidal by the addition of sucrose or some other satisfactory colloid stabilizing material. The product is a slightly hygroscopic, white, granular powder that readily forms an opalescent suspension in water. Such a suspension is bluish white in reflected light, while refracted light produces a reddish color. Colloidal Silver Chloride is used as an antiseptic, especially on mucous membrane.

Toughened Silver Nitrate U.S.P. contains about 5 per cent of AgCl, which acts as a "framework" to hold the molded silver nitrate in form.

Mild Mercurous Chloride U.S.P. contains not less than 99.6 per cent HgCl when dried over sulfuric acid for 5 hours and it must not lose more than 0.5 per cent of its weight when dried in this manner. It is a heavy white powder that is insoluble in water. Mercurous Chloride darkens upon exposure to light due to the formation of metallic mercury. Mercuric Chloride is also produced at the same time. It also turns black by contact with aqueous solutions of calcium hydroxide, ammonia or with sodium or potassium hydroxides. This chemical property is exhibited in the preparation of Black Lotion N.F.

Mercurous Chloride, commonly known as Calomel, is given internally as a purgative. The action is localized in the intestines and is believed to be due to an irritation, probably caused by the small amount of mercuric ions produced in the intestinal fluid. A soluble saline cathartic is usually given after about 6 hours to completely remove the mercury salt from the system. Common forms of dosage are Calomel and Soda Tab-

TABLE 8. METALLIC BROMIDES (M'Br) OF PHARMACEUTICAL IMPORTANCE

Formula	Chemical Name	Solubility (Gm. per cc. at 25° C.)		Characteristics Affecting Storage Requirements
		In Water	In Alcohol	
LiBr	Lithium Bromide	1:0.6	Freely	Deliquescent
NaBr	Sodium Bromide	1:1.2	1:16	Hygroscopic
KBr	Potassium Bromide	1:1.5	1:15	Stable in air
NH_4Br	Ammonium Bromide	1:1.5	1:15	Somewhat hygroscopic

lets, Compound Cathartic Pills and Calomel Tablets, all in the N.F. Calomel is used as an antiseptic, especially in the form of Calomel Ointment N.F. It also may be used as a parasiticide in the form of a powder, being applied as a dust.

The bromides are used medicinally as hypnotics or sedatives. Potassium Bromide is used most frequently, but bromides of other cations are also employed, either alone or in combination.[24]

Lithium Bromide N.F. contains not less than 99 per cent of LiBr when dried at 165° C. for 3 hours. It must not lose more than 15 or less than 10 per cent of its weight when dried under these conditions. The salt is soluble in water, and such solutions are neutral or not more than faintly alkaline to litmus paper. The salt occurs as a white, very deliquescent, granular powder.

Lithium Bromide is used as a hypnotic and sedative. It is an ingredient in Five Bromides Elixir N.F., Bromides Syrup N.F. and it also may be used alone.

Sodium Bromide U.S.P. contains not less than 99 per cent of NaBr after being dried at 110° C. for 4 hours. It must not lose more than 1 per cent of its weight in drying. Sodium Bromide is available as a white, granular powder or as white, cube-shaped crystals. It must be stored in tight containers since it absorbs water, even though it is not deliquescent. Aqueous solutions of the salt are neutral or not more than very slightly alkaline.

Sodium Bromide is used as a hypnotic and sedative. It is an ingredient in Five Bromides Elixir N.F., Three Bromides Elixir N.F., Bromides Syrup N.F. and Three Bromides Tablets N.F. The salt is also in the form of Sodium Bromide Tablets N.F., Sodium Bromide Elixir N.F., as well as in unofficial preparations or alone.

Potassium Bromide U.S.P. contains not less than 99 per cent of KBr after being dried at 110° C. for 4 hours. Like Sodium Bromide, it must not lose more than 1 per cent of its weight when dried under the specified conditions. Potassium Bromide is a white, granular powder or it may occur as cubical crystals. It is stable in air, and storage in well-closed containers is adequate. Aqueous solutions are usually neutral but may be faintly alkaline.

Potassium Bromide is used as a hypnotic and sedative, being used alone in solutions, such as Potassium Bromide Elixir N.F., or in the compound formulations listed under Sodium Bromide.

Ammonium Bromide N.F. contains not less than 99 per cent of NH_4Br after being dried over sulfuric acid for 24 hours. It is a yellowish-white, crystalline powder or it may be in the form of colorless crystals. Ammonium Bromide must be stored in tight containers since it is hygroscopic. The salt

TABLE 9. METALLIC IODIDES (M'I) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water	In Alcohol	
		ALKALI METALS AND AMMONIUM SALTS		
NaI	Sodium Iodide	1:0.6	1:2	Deliquescent with decomposition
KI	Potassium Iodide	1:0.7	1:22	Stable
NH_4I	Ammonium Iodide	1:0.6	1:3.7	Hygroscopic
		HEAVY METALS		
AgI	Silver Iodide	Almost Insoluble	Insoluble	Decomposed by light
HgI	Mercurous Iodide "Yellow Iodide of Mercury"	Insoluble	Insoluble	Decomposed by light

volatilizes completely when ignited, leaving not more than 0.05 per cent residue.

Ammonium Bromide is used as a hypnotic and sedative in the mixed bromide preparations listed under Sodium Bromide and as Ammonium Bromide Elixir N.F.

Iodides. The average human body contains about 25 mg. of iodine in organic combination; about 15 mg. are present in the thyroid gland. Even though this iodine is present in organic combination, a deficiency may be remedied by the administration of a metallic iodide. The iodides also may be used as alteratives and as antisyphilitics.

Soluble iodides form water-soluble triiodide ions (p. 48) with iodine. This property is used extensively in pharmaceutical preparations, such as Iodine Solution U.S.P., and in test solutions such as Wagner's Reagent or the U.S.P. Iodine and Potassium Iodide T.S. The alkali iodides are very soluble in water, forming neutral or faintly alkaline solutions. They are also soluble in alcohol. The iodides of the heavy metals having a valence of 1 are insoluble in the usual solvents. Mercurous and cuprous ions also behave in this manner, as do the mercuric and bismuth ions. Thus, any of the soluble salts of these metals will form insoluble iodides in the presence of iodide ion. Mercuric iodide and bismuth iodide form water-soluble complexes such as K_2HgI_4 and Na_2BiI_5 [26] when an excess of a soluble iodide is added.

Sodium Iodide U.S.P. contains not less than 99 per cent of NaI after being dried to constant weight at 120° C. The loss of weight when dried must not exceed 5 per cent. Sodium Iodide may be obtained as a white, crystalline powder and as colorless, cubical crystals. The salt will deliquesce when exposed to moist air, and a brown color, due to free iodine, usually develops by oxidation. The iodide in sodium iodide is oxidized rather easily to iodine, thus,

$$2NaI + H_2O_2 + H_2SO_4 \text{ (dilute)} \rightarrow I_2 + 2H_2O + Na_2SO_4$$

$$2NaI + 2FeCl_3 \rightarrow 2FeCl_2 + I_2 + 2NaCl$$

Sodium Iodide is prepared in sterile solution and dispensed as Sodium Iodide Ampuls N.F. It is also in the preparation of Iodine Tincture U.S.P. and in Iodine Solution N.F., in which preparations it forms the water-soluble sodium tri-iodide, NaI_3. Sodium Salicylate and Iodide Ampuls N.F. and Sodium Salicylate and Iodide with Colchicine Ampuls N.F. also contain Sodium Iodide.

Potassium Iodide U.S.P. contains not less than 99 per cent of KI after it has been dried for 4 hours at 110° C. The stability of Potassium Iodide upon exposure to air, as contrasted with that of Sodium Iodide, is made apparent when it is noted that the loss in weight on drying of the former salt is limited to a maximum of 1 per cent, whereas the latter may lose as much as 5 per cent and still be U.S.P. quality. Potassium Iodide should be kept in well-closed containers since it does have a slight tendency to deliquesce. The U.S.P. salt is obtainable as large transparent to opaque or white cubical crystals and as a white granular powder.

A saturated solution of Potassium Iodide is prepared by dissolving 100 Gm. in enough distilled water to make 100 cc. This is known as Potassium Iodide Solution N.F. The salt is also made into tablets which are described as Potassium Iodide Tablets in the N.F. Potassium Iodide is used in Strong Iodine Tincture, Iodides Tincture, Iodine Ointment and in Compound Sodium Salicylate and Gelsemium Elixir, all in the N.F. A series of potassium mercuric iodide, K_2HgI_4, solutions are described in the U.S.P.; [26] they are prepared by the addition of a solution of potassium iodide to mercuric iodide, which is dissolved by the presence of an excess of the potassium iodide. The N.N.R. for 1948 [27] also describes a salt, Mercuric Potassium Iodide, which is used as a germicide.

Ammonium Iodide N.F. contains not less than 98 per cent of NH_4I after being dried for 6 hours at 110° C. It also may contain not more than 1 per cent of Ammonium Hypophosphite, which is added as a stabilizing agent (p. 195). Ammonium Iodide is very hygroscopic and develops a yellow to brown color due to the liberation of free iodine if no antioxidant is added; ammonia also is liberated. The U.S.P. salt exists as a white, granular powder and as small, colorless, cubical crystals.

Silver iodide is official in the N.F.[28] as Colloidal Silver Iodide. This preparation contains from 18 to 22 per cent of AgI which has been made colloidally stable by the use of gelatin. It is known as Neo-Silvol (see N.N.R.) and is available as a pale-yellow, granular substance that has a faint odor. The product is freely soluble in water, forming an opalescent colloidal suspension which is milky in appearance. It is most commonly employed as a 10 per cent aqueous solution which is used as an antiseptic on mucous membranes. Such solutions should be freshly prepared and dispensed in light-resistant containers. The halide gradually precipitates from the solution. Colloidal Silver Iodide is affected by light, the silver ion being slowly reduced to metallic silver; for this reason it must be stored in light-resistant containers.

Yellow Mercurous Iodide is described in the N.F.[29] as "a strong yellowish orange, amorphous powder, without odor or taste." It also is known as Protoiodide of Mercury and by the standard chemical name, Mercurous Iodide. The official salt must contain not less than 99 per cent of HgI after being dried over sulfuric acid for 4 hours. It is practically insoluble in water and is insoluble in alcohol and in ether. The compound is decomposed by light, forming a black product, the color being due to finely divided mercury. It must, therefore, be stored in light-resistant containers. A common reaction, used as a qualitative test, is with Sodium Hydroxide T.S., or with Ammonia T.S., which produces a black sub-

stance from which metallic mercury separates on standing. The reaction is represented as

$$2HgI + 2KI \rightarrow K_2HgI_4 + Hg$$

The N.F. describes Yellow Mercurous Iodide Tablets which normally contain 8, 10, 15 and 30 mg. each (approximately equivalent to 1/8, 1/6, 1/4 and 1/2 grains). The compound is used, very rarely, for late stages of syphilis.

Metallic Fluorides. *Sodium Fluoride,* NaF, is the only compound in this group that is of special interest to pharmacists. It is a white powder, but when commercially available for use in the control of cockroaches, it may have a color added as a warning of its toxicity. It is soluble in water in the amount of 1 gram in 25 cc.

Knutson and Armstrong [30] reported in 1944 that dental caries are reduced 40 per cent by topical application of sodium fluoride solution to the teeth of children. A reduction of from 50 to 60 per cent was obtained by the addition of 1 part per million of sodium fluoride to drinking water. The suggested explanation is that the effect is due to the reaction of the fluoride with the tooth surface, thus making it more resistant to decay.[31, 32] Sodium fluoride also has been reported to have given good results in veterinary medicine as an ascaricide for swine.[33]

II. Halides of the Formula $M''X_2$. Halides having the type formula $M''X_2$ are solids at ordinary temperatures. Some of them are very deliquescent and often are heated to form anhydrous, or nearly anhydrous, fused masses. Zinc Chloride, for example, is molded into sticks, and Calcium Chloride is broken into hard fragments or granules. The metals of group II form white halides, with the exception of Red Mercuric Iodide N.F. Certain other metals also form halides having this general formula; thus copper as the cupric ion, iron as the ferrous ion, manganese as the manganous ion, as well as the bivalent ions of tin, lead, platinum and palladium form salts of the general formula $M''X_2$; some of them are colored.

The $M''X_2$ compounds generally are soluble in water, forming neutral or acid solutions. Exceptions to this statement are the fluorides and mercuric iodide since they are almost insoluble in water. Lead Chloride is

Table 10. Metallic Chlorides ($M''Cl_2$) of Pharmaceutical Importance

Formula	Chemical Name	Solubility (Gm. per cc. at 25° C.)		Characteristics Affecting Storage Requirements
		In Water	In Alcohol	
$MgCl_2 \cdot 6H_2O$	Magnesium Chloride	Very soluble	1-2	Deliquescent
$ZnCl_2$	Zinc Chloride	1-0.5, forms acid solution	1-1.5	Deliquescent
$CaCl_2 \cdot 2H_2O$	Calcium Chloride	1-1.2	1-10	Deliquescent
$BaCl_2 \cdot 2H_2O$	Barium Chloride	1-2.8	Insoluble	Stable
$HgCl_2$	Mercuric Chloride "Bichloride of Mercury" "Corrosive Sublimate"	1-13.5	1-3.8	Stable
$FeCl_2$	Ferrous Chloride	1-1	Soluble	Deliquescent
$SnCl_2 \cdot 2H_2O$	Stannous Chloride	1-1	Soluble	Forms basic salt on exposure

soluble in hot water but not in water at ordinary temperatures. Many of this group of halides form crystalline hydrates, e.g., $CaCl_2 \cdot 2H_2O$ and $BaCl_2 \cdot 2H_2O$.

Magnesium Chloride, $MgCl_2 \cdot 6H_2O$, is described as a reagent in the U.S.P. It is used for the preparation of Magnesia Mixture Test Solution; Magnesium Chloride and Ammonium Chloride are dissolved in water and then Ammonia T.S. is added. This test solution is used in the tests for arsenic and phosphorus, forming the compounds $MgNH_4AsO_4 \cdot 6H_2O$ and $MgNH_4PO_4 \cdot 6H_2O$, respectively (p. 172). Magnesium Chloride is produced in the stomach when Milk of Magnesia, Magnesium Carbonate or Magnesium Oxide is taken internally (usually as antacids).

The salt is very deliquescent and it usually occurs as white crystals or in white translucent pieces. It is used in industry for fireproofing wood and for many other purposes.

Zinc Chloride N.F. contains not less than 95 per cent of $ZnCl_2$. It is available in the form of fused sticks or pencils, as porcelain-like masses or as a white (or nearly white) crystalline powder. It is very deliquescent. Its solution in water or alcohol may be slightly turbid but this can be cleared up by the addition of a small amount of hydrochloric acid. Aqueous solutions of Zinc Chloride normally are acid in reaction, due to hydrolysis of the salt according to the reactions:

$$ZnCl_2 + H_2O \rightarrow Zn(OH)Cl + HCl$$
$$2Zn(OH)Cl \rightarrow Zn_2OCl_2 + H_2O$$

The basic salts are responsible for the turbidity in water solution, mentioned above.

Zinc Chloride is used in solution as an escharotic. It is also used in certain solutions for its astringent and antiseptic effect in mouth washes.

Calcium Chloride U.S.P. may contain $CaCl_2$ in amounts varying from 75 to 81 per cent. It is primarily $CaCl_2 \cdot 2H_2O$ which contains 75.5 per cent of the anhydrous salt. The U.S.P. product is white and is in the form of hard fragments or as granules. It is deliquescent. Calcium Chloride is very soluble in water and is used for the preparation of freezing mixtures by mixing it with ice; a temperature of $-45°$ C. is obtainable.

Calcium Chloride is used internally to produce an acid urine since the calcium ion is changed to the comparatively insoluble phosphate. It is also used in the treatment of calcium deficiency, in which case it is generally given intravenously. The salt is also one of the "Three Chlorides" in Ringer's Solution and the preparations made with this solution. Anhydrous Calcium Chloride is used as a dehydrating agent or desiccant.

Barium Chloride N.F. contains not less than 99 per cent of $BaCl_2 \cdot 2H_2O$. It is obtainable as white or colorless crystals or in the form of white granules. The salt is soluble in water but insoluble in alcohol; the other salts in this group are soluble in alcohol. Barium Chloride has all of the properties of the barium ion and the chloride ion. It is therefore incompatible with all of the soluble sulfates, being used as a method of identification of sulfate ions. It is also incompatible with those soluble ions that produce insoluble chlorides.

Barium Chloride is very poisonous. Its principal therapeutic use is in veterinary practice, where it is used to stimulate peristalsis. It may be used also in humans for the alleviation of the symptoms of heart block. Barium Chloride Tablets N.F. are available for veterinary use. Some commercial rodenticides contain Barium Chloride.

Mercuric Chloride N.F. contains not less than 99.5 per cent of $HgCl_2$ after drying for 18 hours over sulfuric acid. The salt is listed in the N.F. as Mercury Bichloride and has the additional synonyms of Corrosive Sublimate and Corrosive Mercuric Chloride. The compound is water-soluble; it forms solutions that are faintly acid but which can be made neutral by the addition of Sodium Chloride.

Mercuric Chloride is only slightly ionized

in water solution, but it exhibits all of the properties of the mercuric ion and the chloride ion. Thus, it will form the insoluble black mercuric sulfide with soluble sulfides; intermediate precipitation of white and yellow mercuric chloride-mercuric sulfide complexes are also observed to form. Soluble iodides form the Red Mercuric Iodide, which is insoluble in water but soluble in an excess of soluble iodide. Alkali hydroxides precipitate Yellow Mercuric Oxide while ammonia, in excess, produces a white precipitate of Ammoniated Mercury. If the ammonia is not kept in excess, a basic compound is produced; possibly a mixture of HgOHCl and $HgNH_2Cl$ is obtained. Reducing agents, as, for example, Stannous Chloride, will form the insoluble Mercurous Chloride. Metals tend to cause mercury to plate out or deposit on the surface; therefore, Mercuric Chloride solutions should not be brought into contact with metallic containers or equipment. Proteins tend to combine with Mercuric Chloride, forming insoluble precipitates.

Mercury Bichloride is used as an antiseptic or disinfectant wash in a concentration of 1-1,000. More dilute solutions also are employed. The N.F. describes Large Bichloride Tablets which contain from 0.42 Gm. to 0.52 Gm. of $HgCl_2$ per tablet. One tablet will make 475 cc. (roughly a quart) of approximately a 1-1,000 solution. The N.F. also describes Small Bichloride Tablets, one of which will make 120 cc. of approximately a 1-1,000 solution. Mercuric Chloride is also used in the N.F. formula for the preparation of Yellow Lotion. The U.S.P. includes a Mercury Bichloride test solution (0.5 N) which is used as a reagent. It will, for example, form a precipitate with certain alkaloids.

Ferrous Chloride is a white crystalline substance when anhydrous, but the tetrahydrate, $FeCl_2 \cdot 4H_2O$, is greenish blue. The salt is very unstable, being rather easily oxidized to the ferric salt. The most important use of this salt is as an intermediate in the preparation of Ferric Chloride Solution and Ferric Chloride. An elixir of Ferrous Chloride has been used as an iron tonic.

Stannous Chloride, $SnCl_2 \cdot 2H_2O$, is described as a reagent in the U.S.P. The compound is freely soluble in water but through hydrolysis tends to form the basic salt, which is not soluble. Thus, the directions for making Stannous Chloride Test Solution in the U.S.P. include the addition of a small amount of hydrochloric acid. An Acid Test Solution is also described; in this 8 Gm. of Stannous Chloride are dissolved in 500 cc. of reagent Hydrochloric Acid.

Stannous Chloride is a strong reducing agent. This property is used in the identification of the mercuric ion. It is used as a reducing agent in organic reactions.

Calcium Bromide N.F. contains from 84 to 94 per cent of $CaBr_2$. It is generally thought to be $CaBr_2 \cdot 2H_2O$. The usual physical appearance is that of white granules. The salt exhibits all of the chemical characteristics of the calcium ion and the bromide ion. Thus, it is incompatible with all

TABLE 11. METALLIC BROMIDES ($M''Br_2$) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water	In Alcohol	
$CaBr_2 \cdot 2H_2O$......	Calcium Bromide	1-0.7	1-1.3	Very deliquescent
$SrBr_2 \cdot 6H_2O$......	Strontium Bromide	1-0.35	Soluble	Deliquescent

soluble sulfates, forming the slightly soluble calcium sulfate. It will also form, for example, the insoluble silver bromide with soluble silver salts. Aqueous solutions of Calcium Bromide are neutral or faintly alkaline.

Calcium Bromide is an ingredient in the N.F. Five Bromides Elixir and the Bromides Syrup. Its general medicinal use is that of a hypnotic or sedative.

Strontium Bromide N.F. consists of not less than 98 per cent of $SrBr_2 \cdot 6H_2O$ and is a deliquescent, crystalline solid. When the salt is dried to constant weight at 200° C., it must not lose more than 32 per cent of its weight. The chemical properties are those of the strontium and bromide ions and its therapeutic properties are those of the bromide ion.

Zinc Iodide N.F. contains not less than 98 per cent of ZnI_2 after being dried over sulfuric acid for 24 hours. When dried in this manner it must not lose more than 5 per cent of its weight. Upon exposure to light and air it deliquesces and becomes brown due to the reaction:

$$2ZnI_2 + O_2 \rightarrow 2ZnO + 2I_2$$

with possible intermediate stages. Its aqueous solution is acid due to hydrolysis.

$$ZnI_2 + H_2O \rightarrow Zn(OH)_2 + 2HI$$

Thus, the liberation of iodine can be explained by the reaction between oxygen and hydriodic acid.

$$4HI + O_2 \rightarrow 2I_2 + 2H_2O \text{ *}$$

The important pharmaceutical preparation containing Zinc Iodide is Iodine and Zinc Iodide Glycerite N.F., which is used in dentistry as an antiseptic.

Ferrous Iodide is not described in either the U.S.P. or the N.F. It is contained in Ferrous Iodide Syrup N.F., which formula suggests the preparation of the ferrous iodide by a chemical reaction between iron and iodine followed by the immediate addition of sugar to the water solution. The ferrous ion, if unprotected, is readily oxidized to the ferric state, resulting in the formation of a basic ferric compound. There is a tendency for iodine to be liberated, due to oxidation, so that hypophosphorous acid is added as a preservative to avoid this reaction in the syrup (p. 168). The N.F. Syrup contains about 7 per cent of ferrous iodide and is used as an iron tonic.

Mercuric Iodide N.F. has the official title of Red Mercuric Iodide to characterize the compound by its color and to differentiate it

TABLE 12. METALLIC IODIDES ($M''I_2$) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water	In Alcohol	
CaI_2	Calcium Iodide	Very soluble	Freely soluble	Deliquescent, decomposes
ZnI_2	Zinc Iodide	1-0.3	Freely soluble	Deliquescent and liberates I_2
FeI_2	Ferrous Iodide	Very soluble	Soluble	Easily oxidized
HgI_2	Mercuric Iodide "Biniodide of Mercury" Red Mercuric Iodide	Insoluble	1-115	Stable in air, affected by light

* See page 26.

from the Mercurous Iodide, which is yellow. It is a "vivid red" powder that contains not less than 99 per cent of HgI_2 when dried for the three-hour period. Mercuric Iodide is practically insoluble in water, but it is soluble in aqueous solutions of soluble iodides. The property is explained by the formation of the soluble complex mercuric tetraiodide ions.

$$HgI_2 + 2KI \rightarrow 2[K]^+ + [HgI_4]^{--}$$

Donovan's Solution N.F. is made by triturating arsenic tri-iodide, which is water-soluble, and Mercuric Iodide in water until solution is effected. This reaction may be explained, at least in part, by the characteristic reaction of the arsenic tri-iodide, acting as a specific example of $M'''X_3$, first hydrolyzing to form hydriodic acid and this in turn forming the soluble H_2HgI_4. Sodium bicarbonate is added and the acids are converted into the more stable sodium salts. The analogous alkali chlorides react to form a soluble complex but the application of some heat is required.

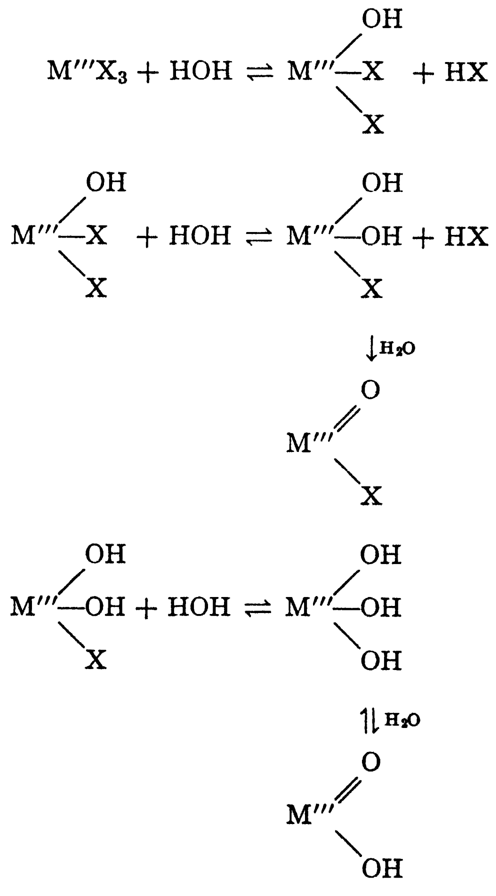
Mercuric Iodide is used in the preparation of Arsenic and Mercuric Iodides Solution N.F. The salt also is employed in veterinary practice for the treatment of enlarged glands, swollen joints, etc. It is not widely used medicinally today, but may be said to have antiseptic properties.

Calcium fluoride is the principal compound in fluorspar, which is used in metallurgy as a flux. It is also used in the manufacture of hydrofluoric acid, certain kinds of glass and enamel. Its medicinal use is extremely limited, having been recommended for the development of teeth and bone structure. Calcium fluoride is used as an insecticide.

The salt is not soluble in water, but will dissolve upon the addition of ammonium chloride. (See Table 13.)

III. Halides of the Formula $M'''X_3$. The halides having this type formula are derived from the elements of groups III, V and VIII and gold from group I. It will be remembered that a few of these elements form other halides, e.g., ferrous halides (FeX_2) and thallous salts (TlX).

The pharmaceutically important $M'''X_3$ compounds are soluble in water, with hydrolysis which results in strongly acid solutions. The reactions may proceed step by step, as indicated by the following general reactions.



Solutions of these salts may develop precipitates but they can be redissolved by the addition of the specific HX obtained in the hydrolysis. The fact that these solutions are strongly acid must be taken into consideration when using them; they not only give the characteristic reactions of the specific metallic ions and halide ions but also behave as acids.

Aluminum Chloride N.F. contains not less than 95 per cent of $AlCl_3 \cdot 6H_2O$ after

TABLE 13. METALLIC FLUORIDES ($M''F_2$) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water	In Alcohol	
CaF_2	Calcium Fluoride	Practically insoluble	Slightly soluble	Stable

being dried over sulfuric acid for 24 hours. It appears as a white or yellowish-white, crystalline powder. The hexahydrate is decomposed into aluminum trioxide, hydrogen chloride and water when heated, according to the reaction

$$2AlCl_3 \cdot 6H_2O \xrightarrow{\Delta} Al_2O_3 + 6HCl + 9H_2O$$

Aluminum chloride is generally used as an external astringent and antiseptic, especially as a deodorant. The N.F. Aluminum Chloride Solution, which is made by dissolving 250 Gm. of Aluminum Chloride in sufficient water to make 1,000 cc. (filtering, if necessary, until a clear solution is obtained), may be used, undiluted, on unbroken and nonirritated skin. Anhydrous aluminum chloride is a catalytic agent, especially in the Friedel-Crafts reaction and in certain industrial reactions, such as the "cracking" of petroleum.

Ferric Chloride, $FeCl_3 \cdot 6H_2O$, is described in the U.S.P. as a reagent. It is an orange-yellow or brown-yellow crystalline salt that is very deliquescent. (The anhydrous salt is a solid made up of black crystalline plates.) Ferric chloride and its solutions should be protected from exposure to light since it may be partly reduced to ferrous chloride.

Ferric chloride is in the N.F. as Ferric Chloride Solution and Ferric Chloride Tincture (Iron Tincture). The Solution contains

TABLE 14. METALLIC CHLORIDES ($M'''Cl_3$) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water *	In Alcohol	
$AlCl_3 \cdot 6H_2O$	Aluminum Chloride	Very soluble Hydrolyzes	1-4	Deliquescent
$FeCl_3 \cdot 6H_2O$	Ferric Chloride "Iron Perchloride"	1-0.25 Hydrolyzes	1-1.2	Deliquescent
$AuCl_3 \cdot 2H_2O$	Auric Chloride	Freely soluble	Freely soluble	Deliquescent
$AsCl_3$	Arsenious Chloride "Arsenic Trichloride"	Soluble Hydrolyzes	Freely soluble	Very hygroscopic
$SbCl_3$	Antimonous Chloride "Antimony Chloride"	Very soluble Hydrolyzes	Soluble	Deliquescent

* These salts are soluble in glycerin.

an equivalent of 10 to 11 per cent of iron and from 3 to 5 per cent of HCl. The Tincture is prepared by mixing 35 cc. of the Solution with enough alcohol to make 100 cc. of the finished product, which contains about 13 Gm. of $FeCl_3$, corresponding to not less than 4.5 Gm. of iron. Both preparations are acid in reaction and have the characteristic yellowish-orange color. Ferric Chloride Solution also is used in making Ferric Citrochloride Tincture N.F. by mixing 35 cc. of it with 15 cc. of water, then dissolving 45 Gm. of Sodium Citrate and finally adding sufficient alcohol to make 100 cc. It is set aside in the cold for a few days. Sodium chloride, which is insoluble in alcohol, separates and is removed by filtration. These solutions are used internally as iron tonics. Ferric Chloride Solution and the Tincture also are used as styptics and astringents.

Ferric Chloride Test Solution U.S.P. is made by dissolving 9 Gm. of $FeCl_3 \cdot 6H_2O$ in sufficient water to make 100 cc. It is a 1 N solution and is used as a reagent. The moderately dilute solutions of salicylates and phenol produce a violet color with Ferric Chloride T.S., thiocyanates produce a red color, benzoates (in neutral solution) produce salmon-colored precipitates and tannic acid yields a bluish-black color or precipitate. Some alkaloids form insoluble double salts with ferric chloride.

Auric Chloride is described in the U.S.P. as a reagent and has the formula $HAuCl_4 \cdot 4H_2O$. It is also known as "Chlorauric Acid" and appears as yellow, hygroscopic crystals that are very soluble in water; they are soluble in alcohol and ether. Anhydrous auric chloride may be prepared by making a solution of gold in chlorine water and careful evaporation to dryness. The anhydrous compound is a brown crystalline substance; it is converted to the insoluble aurous chloride by gentle heating or to gold upon stronger heating. Auric chloride is reduced easily, acting as an oxidizing agent for such ions as the ferrous, stannous and iodide ions.

$$3Fe^{++} + HAuCl_4 \rightarrow 3Fe^{+++} + Au + H^+ + 4Cl^-$$

$$6I^- + 2HAuCl_4 \rightarrow 3I_2 + 2Au + 2H^+ + 8Cl^-$$

$$3Sn^{++} + 2HAuCl_4 \rightarrow 3Sn^{++++} + 2Au + 2H^+ + 8Cl^-$$

Gold Chloride Test Solution U.S.P. is prepared by dissolving 1 Gm. of reagent gold chloride in 35 cc. of water. This solution is used to identify certain alkaloids, e.g., atropine salts, in water solution; it reacts with Gold Chloride T.S. to form a lusterless precipitate.

A solution of $HAuCl_4$ can be neutralized with potassium or sodium hydroxide to form the corresponding salt, e.g., $NaAuCl_4 \cdot 2H_2O$; an excess of alkali will precipitate auric hydroxide, which is yellowish brown. These salts may be used in the synthesis of some gold compounds as well as in photography.

Gold chloride in the form of Gold Sodium Chloride (official in the U.S.P. IX) has been used in arthritis, leprosy, neuralgia and other conditions.

Arsenious Chloride, $AsCl_3$, is not used as such in pharmacy. It is prepared by the action of hydrochloric acid on arsenious oxide. This property is made use of in the preparation of Arsenious Acid Solution N.F. Arsenious trichloride is a colorless liquid. The salt is readily soluble in water, but hydrolyzes so that its solutions are strongly acidic.

Arsenious Acid Solution or "Arsenic Chloride Solution" N.F. contains the equivalent of 1 per cent of As_2O_3 and is used as an acidic solution for the administration of arsenic.

Antimonious Chloride, $SbCl_3$, is commonly known as "Butter of Antimony." Its melting point is 73.4° C. and it is very deliquescent. Antimony trichloride is hydrolyzed by water, forming SbOCl, so that such preparations are strongly acid.

It is used in veterinary practice in the

treatment of a disease commonly known as "poll-evil."

then is washed with hydrochloric acid (sp. gr. 1.12). It also may be prepared by direct

TABLE 15. METALLIC BROMIDES ($M'''Br_3$) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS AFFECTING STORAGE REQUIREMENTS
		In Water	In Alcohol	
$AuBr_3$........	Auric Bromide	Soluble	Soluble with gradual reduction	Deliquescent

combination of arsenic and iodine, either by application of heat or by interaction in carbon disulfide solution. The compound volatilizes when heated to temperatures above 100° C.; this is made the basis of an N.F. test for purity.

Arsenic Tri-iodide is used as a tonic and as an alterative combining the effects of both the arsenic and the iodide ions. The compound is used to make the well-known Donovan's Solution which is in the N.F. as Arsenic and Mercuric Iodides Solution. It contains the equivalent of Arsenic Tri-iodide and Red Mercuric Iodide. In the preparation the two compounds are mixed and dissolved in water, the probable reaction being:

$$AsI_3 + HgI_2 \rightarrow AsI_3 \cdot HgI_2 \xrightarrow{3H_2O}$$

$$As(OH)_3 + H_2\,(HgI_4) + HI$$

The solution then is neutralized by the addition of sodium bicarbonate and diluted to the proper concentration.

Arsenic Tri-iodide and Donovan's Solution are affected by light.

Auric bromide is prepared in the form of an elixir and is used as an antispasmodic in the treatment of whooping cough and similar conditions. Bromauric Acid, $HAuBr_4 \cdot 5H_2O$, was official in N.F. V.

Metallic Iodides ($M'''I_3$) of Pharmaceutical Importance. Arsenic Tri-iodide N.F. (AsI_3) is also known as arsenious iodide. It is an orange to red, crystalline powder that is soluble in water (1 Gm. in 12 cc.) with almost complete hydrolysis.

$$AsI_3 + 3H_2O \rightarrow As(OH)_3 + 3HI$$

An aqueous solution may develop a brown color due to the liberation of iodine from the hydriodic acid.

$$4HI + O_2 \rightarrow 2I_2 + 2H_2O$$

This reaction is made the basis for one of the identification tests for Arsenic Tri-iodide in the N.F., except that ferric chloride is used as the oxidizing agent.

$$2HI + 2FeCl_3 \rightarrow I_2 + 2HCl + 2FeCl_2$$

Arsenic Tri-iodide is soluble in alcohol, chloroform and ether.

The compound may be made by interaction between arsenic trichloride, in concentrated hydrochloric acid, and potassium iodide. The arsenic trichloride solution is poured into a concentrated solution of potassium iodide in water. The precipitate

IV. HALIDES OF THE FORMULA $M''''Cl_4$. Carbon tetrachloride normally is considered as a substitution product of methane, and as such is included in the study of organic compounds. In an analogous manner, silicon tetrachloride may be regarded as a substitution product of silane; however, it may be

prepared by the direct action of chlorine on silicon, a property common to the elements of group IV with the exception of carbon. It may also be formed according to the reaction:

$$SiO + 2C + 2Cl_2 \rightarrow SiCl_4 + 2CO$$

All of the tetrachlorides are volatile liquids and are properly designated as chloranhydrides rather than salts. Silicon tetrachloride is decomposed readily by water, with the production of hydrochloric acid and silicic acid $[SiO(OH)_2]$. Stannic chloride ($SnCl_4$), germanic chloride ($GeCl_4$) and plumbic chloride ($PbCl_4$) are stable in aqueous solution only when there is an excess of hydrochloric acid; otherwise, they decompose in a manner similar to silicon tetrachloride. None of these, except CCl_4, compounds is of any special significance in pharmacy; this statement is also true of the other $M''''X_4$ compounds.

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5

Hydroxides (Oxyacids) of Group VII and Their Salts of Pharmaceutical Importance

HEPTAHYDROXIDES OF THE HALOGENS AND MANGANESE
PENTAHYDROXIDES OF THE HALOGENS
TRIHYDROXIDES OF THE HALOGENS
MONOHYDROXIDES OF THE HALOGENS

As noted under their chemical properties (p. 33), the halogens exhibit valences of seven, five, three and one toward electronegative elements or groups of elements. If these valences are satisfied by the electronegative hydroxyl (—OH) group, there may be heptahydroxides, pentahydroxides, trihydroxides and monohydroxides of the halogens. These, or their partial dehydration products, are the so-called halogen oxyacids. On the following pages a summary of all of these compounds will be given in condensed table form.

HEPTAHYDROXIDES OF THE HALOGENS AND MANGANESE

With X as the general symbol for the elements of group VII of the periodic table acting in their heptavalent state, the following heptahydroxides and their partial and complete dehydration products, together with their names, are indicated as follows:

$X(OH)_7$ Hepta-hydroxide	$XO(OH)_5$ Monoxide-pentahydroxide	$XO_2(OH)_3$ Dioxide-trihydroxide	XO_3OH Trioxide-monohydroxide ("Per-ic" Acid)	X_2O_7 Heptoxide ("Per-ic" Acid Anhydride)
$Cl(OH)_7$	$ClO(OH)_5$	$ClO_2(OH)_3$	ClO_3OH * Perchloric acid	Cl_2O_7 Chlorine heptoxide (Perchloric acid anhydride)
$Br(OH)_7$	$BrO(OH)_5$	$BrO_2(OH)_3$	BrO_3OH Perbromic acid	Br_2O_7 Bromine heptoxide (Perbromic acid anhydride)
$I(OH)_7$	$IO(OH)_5$	$IO_2(OH)_3$	IO_3OH * Periodic acid	I_2O_7 Iodine heptoxide (Periodic acid anhydride)
$Mn(OH)_7$	$MnO(OH)_5$	$MnO_2(OH)_3$	MnO_3OH * Permanganic acid	Mn_2O_7 Manganese heptoxide (Permanganic acid anhydride)

* Compounds that are of pharmaceutical importance and are represented in the U.S.P. or N.F., either as such or in the form of their salts.

It will be noted that the heptahydroxide of manganese is included in this table because of the fact that when manganese acts as a heptavalent element, it resembles the halogens in many respects.

Only a few of the compounds indicated in the above table are known and still fewer are of pharmaceutical interest. Perchloric acid, $HClO_4$; its salts, the perchlorates; its hydrates and its anhydride, chlorine heptoxide Cl_2O_7, are all known. Perchloric acid, in 70 per cent strength, and potassium perchlorate are included in the U.S.P. Reagents, and the latter is also formed as one of the products when Potassium Chlorate N.F. is heated (p. 58). While the hypothetical periodic acid anhydride or iodine heptoxide, I_2O_7, is not known, some of the hydrates of periodic acid, with their salts, the periodates, are known. Periodic acid is represented in the N.F. Reagents in its M/10 solution and as the salt, *p*-sodium periodate, $Na_3H_2IO_6$. Permanganic acid is represented in the U.S.P. by its familiar salt, Potassium Permanganate, as such and in N/10 and N/100 volumetric solutions.

While perchloric acid, $HClO_4$, is the trioxide-monohydroxide, ClO_3OH, periodic acid is more commonly known as the monoxide-pentahydroxide, $IO(OH)_5$, as H_5IO_6, or the dihydrate, $HIO_4 \cdot 2H_2O$. An acid of the formula HIO_4 has not been well characterized, and periodate salts of the formulas $M'_2H_3IO_6$ and M'_5IO_6, in which either two or all five hydrogens of the dihydrate are replaced by metals, are well known.

The nomenclature commonly used for the various perhalic acids and their salts, the perhalates, may be illustrated with the periodic acids and periodates:

IO_3OH HIO_4, Meta-Periodic Acid

$AgIO_4$, Silver Meta-Periodate

$IO_2(OH)_3$ H_3IO_5, Meso-Periodic Acid

Ag_3IO_5, *n*-Silver Meso-Periodate

$IO(OH)_5$ H_5IO_6, Para-Periodic Acid

Ag_5IO_6, *n*-Silver Para-Periodate

$Ag_2H_3IO_6$, sec-Silver Para-Periodate

$I(OH)_7$ H_7IO_7, Ortho-Periodic Acid

No Salts Known

The use of the Greek prefixes ortho and meta to designate acids formed from an anhydride by varying amounts of hydration will be encountered later under the hydroxides of the elements of group V (p. 167). When an anhydride forms a series of acids by combining with different amounts of water, the acid containing the most water is called the ortho-acid, from the Greek word meaning regular; the one containing the least water is called the meta-acid, from the Greek word meaning beyond (less than the highest). The prefixes, para and meso, come from the Greek words meaning beside and middle or intermediate, respectively.

Perbromic acid is not known to exist.

Methods of Preparation, Properties and Uses. Perchloric acid is formed when chloric acid, $HClO_3$, is allowed to decompose spontaneously at ordinary temperature, and more rapidly when it is heated. In a similar way, chlorates upon heating yield, in part, perchlorates, from which the free acid may be obtained by the action of concentrated sulfuric acid:

$$4KClO_3 \xrightarrow{\Delta} KCl + 3KClO_4$$

Further heating results in a loss of oxygen from the perchlorate, leaving a residue of the chloride:

$$3KClO_4 \xrightarrow{\Delta} 3KCl + 6O_2$$

This reaction is used as a test for identity of the N.F. Potassium Chlorate.[1]

Periodic acid may be prepared by the electrolytic oxidation of a mixture of iodine and iodic acid, while its salts, the periodates, may be made by oxidation of the corresponding iodate salt in alkaline solution by chlorine gas.

Anhydrous perchloric acid is little known because it is unstable and highly explosive at ordinary temperatures. However, it is available as a reagent in concentrations up to 70 per cent. Both perchloric and periodic acids form salts which usually are only slightly soluble in water. While not espe-

cially active in the cold, a hot, concentrated solution of perchloric acid is a powerful oxidizing as well as dehydrating agent and is used for such purposes. Magnesium perchlorate is a widely used and efficient dehydrating agent sold under such trade names as Dehydrite, Anhydrone, etc., while barium perchlorate and mixtures of it with the magnesium salt are also used as drying agents. Perchloric and periodic acids and their salts are finding increasing use as reagents in quantitative analytical chemistry.

Permanganic acid, $HMnO_4$, is formed when the calculated quantity of sulfuric acid is added to barium permanganate; barium is precipitated as the sulfate and leaves a deep reddish-purple solution of permanganic acid:

$$Ba(MnO_4)_2 + H_2SO_4 \rightarrow BaSO_4 + 2HMnO_4$$

If allowed to stand or if treated with cold, concentrated sulfuric acid, the permanganic acid is dehydrated to the corresponding manganese heptoxide, permanganic acid anhydride, which forms a dark-green, oily solution:

$$2HMnO_4 \rightarrow H_2O + Mn_2O_7$$

Both the acid and the anhydride are strong oxidizing agents and will liberate oxygen with explosive violence at elevated temperatures.

Permanganic acid is best known in the form of its salt, potassium permanganate. This commonly is prepared by the oxidation of manganese dioxide with potassium hydroxide and potassium chlorate or nitrate to potassium manganate, which is in turn converted to the permanganate by the action of water and carbon dioxide:

$$3MnO_2 + 6KOH \rightarrow 3K_2MnO_3 + 3H_2O$$

$$3K_2MnO_3 + KClO_3 \rightarrow 3K_2MnO_4 + KCl$$

$$3K_2MnO_4 + 2CO_2 + H_2O \rightarrow 2KMnO_4 + MnO_2 \cdot H_2O + 2K_2CO_3$$

Potassium permanganate, like the corresponding salt potassium perchlorate, is a powerful oxidizing agent and readily gives up oxygen when it comes in contact with readily oxidizable substances, especially organic material, and the U.S.P. prescribes caution in its handling.[2] It does not, however, part with all of its oxygen and its action is controlled fairly easily; therefore, it furnishes a valuable reagent for oxidizing purposes, especially in quantitative analytical work.

As an oxidizing agent, potassium permanganate acts in several different ways. When heated alone, it gives off oxygen and changes to potassium manganate and manganese dioxide:

$$2KMnO_4 \xrightarrow{\Delta} K_2MnO_4 + MnO_2 + O_2$$

In neutral or alkaline solution, potassium permanganate *acts as though* it liberates oxygen, with the formation of a precipitate of manganese dioxide, more or less hydrated, and potassium hydroxide:

$$2KMnO_4 + H_2O \rightarrow 2MnO_2 + 2KOH + 3O$$

In this reaction for each two molecules of permanganate three atoms of oxygen are available for oxidizing purposes. Potassium permanganate behaves according to this reaction when brought in contact with organic compounds or readily oxidizable substances. Thus, the oxidation of methyl alcohol to formaldehyde by means of permanganate might be expressed as follows:

$$2KMnO_4 + 3CH_3OH \rightarrow 2MnO_2 + 2KOH + 2H_2O + 3HCHO$$

Likewise the oxidation of a double bond, e.g., the oxidation of ethylene to ethylene glycol might be expressed by a similar reaction:

$$2KMnO_4 + 3CH_2{=}CH_2 + 4H_2O \rightarrow 2MnO_2 + 2KOH + 3CH_2OH{-}CH_2OH$$

It is this type of reaction that forms the basis of the Baeyer test for the double-bond in an organic compound, the oxidation being evidenced by a change in color of the purple permanganate solution.

Another example of this type of oxidation by permanganate in alkaline solution is found in the oxidation of potassium iodide to potassium iodate:

$$2KMnO_4 + KI + H_2O \rightarrow 2MnO_2 + 2KOH + KIO_3$$

Use of this reaction has already been referred to (p. 32) in the assay of organic iodine compounds, where the organic iodine is converted, by fusion with potassium carbonate, into potassium iodide, which is oxidized to iodate in the above manner.

The above reactions, involving the liberation of oxygen from potassium permanganate in neutral or alkaline solution, take place with noticeable rapidity only in the presence of reducing agents, i.e., when something is present to accept and utilize the available oxygen; therefore, a tenth-normal solution of potassium permanganate made from absolutely pure water and protected from all accidental impurities should remain fairly stable and should require restandardization only at infrequent intervals. Such conditions are difficult to realize. In order to approach them as closely as possible, the U.S.P. directs that Potassium Permanganate, Tenth-Normal, be prepared and boiled for about 15 minutes, and then allowed to stand for at least two days before being filtered through asbestos and standardized.[8] This is done in order that all impurities in the distilled water and on the surface of the flask may be completely oxidized. Boiling facilitates the oxidation, and an even longer period of standing is advisable when possible. If the solution is to be diluted after standardization, this should be done with distilled water which has been redistilled over potassium permanganate. All apparatus used should be cleaned by washing with a solution containing potassium permanganate acidulated with sulfuric acid and then rinsed with water which has been redistilled as mentioned. The solution should be preserved in amber-colored bottles provided with well-fitting glass stoppers; only burettes with glass stopcocks should be used in titrations with this reagent since cork or rubber stoppers and rubber connections might be oxidized by the solution and thus affect its strength. If these precautions are not observed, the solution must be restandardized frequently.

When potassium permanganate is used as an oxidizing agent for quantitative analytical work it is always used in acid solution. The reaction that takes place under acid conditions is not only more efficient than it is in neutral or alkaline solution, but also only colorless, soluble compounds are formed; the disappearance of the purple color of the permanganate solution marks the end of the reaction and no other indicator is necessary. The reaction of permanganate in acid solution may be expressed as follows:

$$2KMnO_4 + H_2SO_4 \rightarrow K_2SO_4 + 2HMnO_4$$

If no reducing agent is present, this is as far as the reaction proceeds, and since the solution of permanganic acid is the same color as that of its potassium salt, no visible change is observed. In the presence of a reducing agent, however (i.e., some substance which will accept or utilize the oxygen), the permanganic acid *makes available* the greater part of its oxygen:

$$2HMnO_4 \rightarrow H_2O + 2MnO + 5O$$

The manganous oxide thus formed is basic and combines at once with the excess of sulfuric acid, giving a colorless solution of manganous sulfate:

$$2MnO + 2H_2SO_4 \rightarrow 2MnSO_4 + 2H_2O$$

The sum total of the above reactions may be written as one:

$$2KMnO_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 3H_2O + 5O$$

Hence, for every two molecules of potassium permanganate employed *it may be considered* that five atoms of oxygen are available for oxidizing purposes. From this reaction it is seen that the gram equivalent weight of potassium permanganate, i.e., the amount equivalent to 1.008 Gm. of hydrogen or 8.000 Gm. of oxygen, is one-fifth of its molecular weight, or $KMnO_4/5$.

The use of potassium permanganate as a quantitative oxidizing agent in many of the U.S.P. and N.F. assays will be taken up later (p. 96).

Because of its oxidizing power, especially toward organic substances, potassium permanganate is used in medicine in dilute solutions externally as an antiseptic and disinfectant, by application to the skin, and by injection and irrigation in the urethra and other body passages and cavities.

PENTAHYDROXIDES OF THE HALOGENS

With X as the general symbol for the halogens acting in their pentavalent state, the following pentahydroxides and their partial and complete dehydration products, together with their names, are indicated as follows:

$X(OH)_5$ Penta-hydroxide	$XO(OH)_3$ Monoxide-trihydroxide	XO_2OH Dioxide-monohydroxide ("-ic" Acid)	X_2O_5 Pentoxide ("-ic" Acid Anhydride)
$Cl(OH)_5$	$ClO(OH)_3$	ClO_2OH * Chloric acid	Cl_2O_5 Chlorine pentoxide (Chloric acid anhydride)
$Br(OH)_5$	$BrO(OH_3)$	BrO_2OH * Bromic acid	Br_2O_5 Bromine pentoxide (Bromic acid anhydride)
$I(OH)_5$	$IO(OH)_3$	IO_2OH * Iodic acid	I_2O_5 * Iodine pentoxide (Iodic acid anhydride)

* Compounds that are of pharmaceutical importance and are represented in the U.S.P. or N.F., either as such or in the form of their salts.

Like the heptahydroxides, the pentahydroxides of the halogens do not appear to exist as such; moreover, little is known of their first dehydration products corresponding to the general formula $XO(OH)_3$. Representatives of their second dehydration products, corresponding to the general formula XO_2OH, are of importance in pharmacy; they occur as salts in the U.S.P. or N.F. or are formed in tests for identity and purity.

Chloric acid is represented as its salt, Potassium Chlorate, in the N.F. as monograph; it also is represented in Potassium Chlorate Tablets and Potassium Chlorate Gargle with Iron in the N.F.

Bromic acid is represented as its salt, Potassium Bromate, in the U.S.P. reagents as well as in its tenth-normal solution; it is used in the preparation of Bromine, Tenth-Normal (Koppeschaar's Solution).

Iodic acid is included in the N.F. reagents; also as its salt, Potassium Iodate, in the U.S.P. reagents, as well as in several volumetric solutions in both the U.S.P. and N.F. It also is represented in the form of its anhydride, Iodine Pentoxide (Iodic Anhydride) in the U.S.P. reagents.

Methods of Formation and Preparation. Since the "hal-ic" acids usually are formed from their corresponding salts, the "hal-ates," methods of formation and preparation of the two will be taken up together, the acids being considered first.

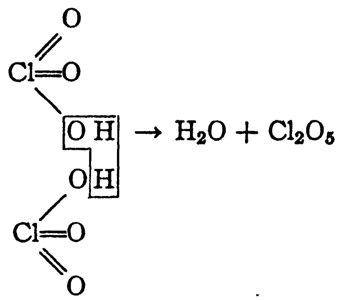
I. Action of an Acid upon a Metallic Halate.

A. 1. $KClO_3 + HCl \rightarrow KCl + HClO_3$

This is the first reaction which takes place when an acid reacts with a metallic halate, and the above reaction occurs in the test for identity of Potassium Chlorate.[4] The chloric acid, however, is unstable and reacts with the excess of hydrochloric acid present with the formation of water and chlorine:

$$HClO_3 + 5HCl \rightarrow 3H_2O + 3Cl_2$$

This, however, is not the only reaction taking place. Two molecules of chloric acid may interact, and usually do, to form water and chlorine pentoxide:



The chlorine pentoxide, in the presence of hydrochloric acid, breaks down to form lower oxides of chlorine:

$$Cl_2O_5 \rightarrow Cl_2O_3 + O_2$$

$$Cl_2O_3 \rightarrow Cl_2O + O_2$$

Hence, such a reaction mixture will evolve not only chlorine but also oxides of chlorine.[4] This is why the extemporaneous chlorine water prepared in this way (p. 30) was not considered the same as Chlorine Water.[5]

2. $2KClO_3 + H_2SO_4 \rightarrow K_2SO_4 + 2HClO_3$

If sulfuric acid is used in place of hydrochloric acid, the first reaction is the same. In this case, however, the oxides of chlorine are formed almost exclusively. Since sulfuric acid is a strong dehydrating agent, the dehydration of the chloric acid and subsequent breakdown of the oxides of chlorine takes place much more rapidly and violently than with hydrochloric acid, usually with explosive violence. Hence, concentrated sulfuric acid should be added to potassium chlorate with great caution.[6]

B. $2LiBrO_3 + H_2SO_4 \rightarrow Li_2SO_4 + 2HBrO_3$

In the test for bromate as impurity in Lithium Bromide N.F. the above reaction will take place if bromate is present. At the same time, the sulfuric acid reacts with the bromide to form hydrobromic acid, and the latter, reacting with the bromic acid, liberates bromine, which is detected by a yellow color:[7]

$$HBrO_3 + 5HBr \rightarrow 3H_2O + 3Br_2$$

If there is no bromate present as impurity, the first reaction naturally cannot take place and no yellow color of bromine appears at once. Bromine, however, may be liberated upon standing due to oxidation of the hydrobromic acid by sulfuric acid (p. 43); hence, the N.F. specifies that the yellow color must be produced immediately.

The same reactions are involved in testing other metallic bromides of the U.S.P. and N.F. for a bromate impurity. Since the metallic bromide and bromate are prepared by the same reaction (pp. 56, 80) and are separated by their difference in solubility, each is likely to accompany the other as impurity and it is necessary to provide a test for metallic bromide impurity in the metallic bromate as well as for a bromate impurity in the bromide. The same reactions, as shown, are made use of in both tests (p. 30).

C. $2KIO_3 + H_2SO_4 \rightarrow K_2SO_4 + 2HIO_3$

Like the analogous reactions in B, this reaction occurs if iodate is present in Potassium Iodide U.S.P. when it is tested for an impurity,[8] and if iodide is present in Potassium Iodate.[9] The iodic acid reacts

at once with hydriodic acid, liberating iodine, which colors the solution yellow or a chloroform layer violet. The color should be produced within a minute since iodine may be liberated on longer standing by the oxidizing action of sulfuric acid upon the hydriodic acid (p. 43).

II. Oxidation of Halogen of Higher Atomic Weight by Halogen of Lower Atomic Weight or Other Oxidizing Agent. This method, which is applicable to the formation of both bromic and iodic acids, will be illustrated with examples involving the latter.

A. $I_2 + 5Cl_2 + 6H_2O \rightarrow 2HIO_3 + 10HCl$

This reaction occurs when iodine is acted on by an excess of chlorine water and partly explains why, in the use of chlorine water to test for the identity of iodides, the chlorine water must be added carefully, avoiding an excess (p. 28).

B. $3I_2 + 5KClO_3 + 3H_2O \rightarrow 6HIO_3 + 5KCl$

Iodine is oxidized to iodic acid by an aqueous solution of potassium chlorate. Chloric acid will accomplish the same thing. Iodine monochloride is oxidized even more easily by potassium chlorate:

$$ICl + KClO_3 \rightarrow KIO_3 + Cl_2$$

This reaction takes place when chlorine is passed into a suspension of iodine in water and potassium chlorate is added.

C. $I_2 + 10HNO_3 \rightarrow 2HIO_3 + 10NO_2 + 4H_2O$

Iodic acid may be prepared by the direct oxidation of iodine with nitric acid, although the reaction is probably more complex than shown above. Powdered iodine is added in divided portions to concentrated nitric acid; a current of air or carbon dioxide is passed through the mixture to remove the oxides of nitrogen. After the iodine has dissolved and its color has disappeared, the mixture is allowed to cool, and the iodic acid which separates is filtered off and recrystallized from dilute nitric acid.

III. Action of Heat on a Hypohalite.

A. When halogen is added to a cold solution of metallic hydroxide, the reaction takes place as follows (p. 56):

$$2M'OH + X_2 \rightarrow H_2O + M'X + M'OX$$

with the formation of one molecule of metallic halide and one of metallic hypohalite. If the above solution then is boiled, one molecule of the hypohalite is oxidized, at the expense of two other molecules, to metallic halate, the other two molecules being reduced to halide:

$$3M'OX \xrightarrow{\Delta} M'O_3X + 2M'X$$

Since for each molecule of hypohalite formed in the first reaction there is formed also a molecule of halide and since it takes three molecules of hypohalite to produce one of halate in the second reaction, it follows that for each molecule of metallic halate produced five molecules of metallic halide are formed at the same time:

$$3M'OX + 3M'X \xrightarrow{\Delta} M'O_3X + 5M'X$$

Consequently, this method is used for the preparation of both metallic halates and metallic halides (p. 56). The halate, being more insoluble, is crystallized first from the resulting solution, and unless great care is used in its purification, it is liable to be contaminated by the presence of the corresponding halide. By the same token, metallic halide prepared in this way may be contaminated by the presence of the corresponding halate, hence the necessity of testing for the presence of each as impurity in the other (p. 57). It will be noted that no test for chlorate impurity is given in the U.S.P. under either Sodium Chloride or Potassium Chloride but that a test for bromate impurity is included under Sodium Bromide and one for iodate impurity is included under Sodium Iodide. The reason for this is apparent from the fact that sodium chlo-

ride and potassium chloride are obtained from natural sources and, therefore, are not liable to be contaminated by the chlorate introduced by this method of preparation.

Since the demand for metallic bromates and iodates is small when compared with that for the corresponding bromides and iodides, much of the bromate and iodate formed according to the above reaction is reduced to the corresponding bromide and iodide by heating with carbon (p. 57):

$$M'O_3X + 3C \xrightarrow{\Delta} M'X + 3CO$$

The reduction may not always be absolutely complete, and bromate or iodate may remain as an impurity in the resulting bromide or iodide.

B. If Potassium Chlorate N.F. were prepared according to the above reaction, starting with potassium hydroxide and chlorine, there would result five molecules of potassium chloride for each molecule of the chlorate. Since, however, the potassium chloride obtained here as a by-product is of little value because of its plentiful existence in nature (p. 22) and also because this method necessitates the use of expensive potassium hydroxide, it is modified by first preparing calcium chlorate by the action of chlorine on less expensive slaked lime and heating and then obtaining potassium chlorate by a double decomposition between the calcium chlorate and inexpensive potassium chloride:

$$6Ca(OH)_2 + 6Cl_2 \rightarrow 6H_2O + 6CaClOCl \xrightarrow{\Delta} Ca(O_3Cl)_2 + 5CaCl_2$$

$$Ca(O_3Cl)_2 + 2KCl \rightarrow 2KClO_3 + CaCl_2$$

The calcium chloride thus obtained as a by-product is also of more value (p. 66) than the potassium chloride that would be obtained by the usual method.

C. Metallic halates, including potassium chlorate, also are prepared on a commercial scale according to the general reaction cited under A, but under modified conditions. A hot, aqueous solution of potassium chloride is electrolyzed in a cell in which the anode and cathode are not separated, thus, the potassium hydroxide and chlorine which are formed come into contact in the electrolytic cell (p. 23), with the formation of potassium chlorate and potassium chloride:

$$2KCl + 2HOH \xrightarrow{\text{electrolysis}} 2KOH + Cl_2 + H_2$$

$$2KOH + Cl_2 \rightarrow KCl + KOCl + H_2O$$

$$3KCl + 3KOCl \xrightarrow{\Delta} KClO_3 + 5KCl$$

The sparingly soluble potassium chlorate settles out as a crystalline deposit, leaving the potassium chloride in solution, where it can again be electrolyzed with the formation of more chlorate, the process being more or less continuous in nature. In a modification of this process, sodium chlorate first is prepared by electrolysis of sodium chloride and then is converted into potassium chlorate by double decomposition with potassium chloride. This electrolytic process is used extensively wherever water power and electricity can be obtained cheaply.

Properties and Uses. Pure anhydrous chloric and bromic acids are not commonly obtained because of their tendency to decompose. In concentrated solutions they are colorless, viscid liquids with a pungent smell; they decompose upon exposure to light, more rapidly and violently at elevated temperatures, and also in the presence of organic matter. Iodic acid, on the other hand, is more stable and can be obtained as a white crystalline solid, readily soluble in water, which is less easily decomposed by heat and, in fact, can be converted into its anhydride, I_2O_5, upon heating. Iodine pentoxide likewise is a stable white powder, decomposing into iodine and oxygen at its melting point, and dissolving readily in water to form iodic acid.

All three acids are "acid" in character, forming salts by replacement of the hydrogen by metal. Chloric and bromic acids form only normal salts of the formula $M'XO_3$,

while iodic acid forms a series of acid iodates, such as $M'H(IO_3)_2$, $M'H_2(IO_3)_3$, giving evidence of the existence of polybasic iodic acids of a polymerized form. The normal salts of the acids, the "hal-ates," generally are soluble in water, although potassium chlorate is the least soluble of any of them.

In general, compounds of halogen with oxygen, in which the halogen is present as a pentavalent element, are good oxidizing agents. Furthermore, the stability of compounds of the halogens with oxygen increases with an increase in the atomic weight of the halogen concerned. Thus, the compounds of oxygen with iodine are the most stable, those with bromine less and those with chlorine are least stable (p. 33), i.e., as oxidizing agents $KClO_3 > KBrO_3 > KIO_3$. (Compounds of fluorine with oxygen are not commonly known.) In conformity with this general statement, the U.S.P. does not include any such precautions for the handling of Potassium Bromate and Potassium Iodate as it does for Potassium Chlorate.

The ways in which compounds like potassium perchlorate and potassium permanganate give up oxygen have already been discussed (p. 75). Compounds like potassium chlorate, in which halogen is present as a pentavalent element, may oxidize in two different ways: (1) by the liberation of oxygen, and (2) by the liberation of halogen.

I. By the Liberation of Oxygen.

A. It has already been shown that potassium chlorate when heated readily decomposes to form potassium perchlorate and potassium chloride (p. 58):

$$4KClO_3 \xrightarrow{\Delta} 3KClO_4 + KCl$$

At the same time, however, a part of the potassium chlorate decomposes with the liberation of oxygen:

$$2KClO_3 \xrightarrow{\Delta} 2KCl + 3O_2$$

At a higher temperature, the potassium perchlorate, formed in the first reaction, is decomposed further, with the liberation of more oxygen:

$$3KClO_4 \xrightarrow{\Delta} 3KCl + 6O_2$$

The use of a catalyst accelerates the decomposition of potassium chlorate and causes the smoother liberation of oxygen at a lower temperature. These reactions are commonly used as a laboratory method for the preparation of oxygen by first mixing manganese dioxide (free from organic matter!) with the potassium chlorate before it is heated.

B. When potassium chlorate is triturated with substances that are oxidized easily (organic material of any sort, sulfur, sulfides, hypophosphites, etc.), its oxidizing power becomes manifest; the oxidation often takes place with such violence that dangerous explosions occur. Therefore, great care should be observed in handling the compound.[10] The use and value of Potassium Chlorate N.F. as an antiseptic, throat gargle, etc., in medicine undoubtedly is due largely to its oxidizing property. Likewise, this property makes it useful in the preparation of matches and explosive pyrotechnics.

C. An example of the use of potassium chlorate as an oxidizing agent in qualitative analysis is found in the test for arsenic impurity in Reduced Iron as carried out according to the directions of the U.S.P. XI.[11] After the iron has been brought into solution with sulfuric acid, any particles of arsenic left undissolved in the residue are changed to the oxide by oxidation with potassium chlorate:

$$2As + KClO_3 \rightarrow As_2O_3 + KCl$$

D. An example of the quantitative application of the oxidizing property of this compound is found in the assay of Potassium Chlorate, U.S.P. Reagents.[12] Here the salt oxidizes the ferrous iron in acid ferrous sulfate solution to ferric iron:

$$KClO_3 + 6FeSO_4 + 3H_2SO_4 \rightarrow 3Fe_2(SO_4)_3 + KCl + 3H_2O$$

Further details of this assay will be taken up later (p. 96).

E. In the assay of Potassium Chlorate N.F., a further example of its oxidizing property by liberation of oxygen is exhibited.[10] A weighed sample is allowed to oxidize nitrous acid, and the potassium chloride resulting is determined in the usual manner:

$$KClO_3 + 3HNO_2 \rightarrow 3HNO_3 + KCl$$

The same oxidizing property is made use of in the U.S.P. identification tests for chlorates.[18] Chlorates are not precipitated by Silver Nitrate T.S., but in the presence of sulfurous acid they will give a white precipitate of silver chloride, due to the liberation of potassium chloride through an oxidation reaction:

$$KClO_3 + 3H_2SO_3 \rightarrow 3H_2SO_4 + KCl$$

F. The reduction of metallic bromates and iodates to the corresponding bromides and iodides (pp. 57, 81) by heating them with carbon makes use of their oxidizing property by loss of oxygen. This same reaction is used in one of the U.S.P. identification tests for bromates.[18]

II. By the Liberation of Halogen. Metallic halates act indirectly as oxidizing agents through the liberation of halogen. When the corresponding hydrogen halide is added to a mixture of metallic halide and metallic halate, halogen is evolved; this may act as an oxidizing agent directly or through its reaction with water, by which it liberates oxygen. Examples of these reactions have already been discussed (p. 30).

TRIHYDROXIDES OF THE HALOGENS

With X as the general symbol for the halogens acting in their trivalent state, the following trihydroxides and their partial and complete dehydration products, together with the names, are indicated as follows:

$X(OH)_3$ Trihydroxide	$XO(OH)$ Monoxide-monohydroxide ("-ous" Acid)	X_2O_3 Trioxide ("-ous" Acid Anhydride)
$Cl(OH)_3$	$ClO(OH)$ Chlorous acid	Cl_2O_3 Chlorine trioxide (Chlorous acid anhydride)
$Br(OH)_3$	$BrO(OH)$ Bromous acid	Br_2O_3 Bromine trioxide (Bromous acid anhydride)
$I(OH)_3$	$IO(OH)$ Iodous acid	I_2O_3 Iodine trioxide (Iodous acid anhydride)

Little is known of the above compounds. None of the acids is known in the free state; chlorous acid is known in the form of its salts, the chlorites. None of the trioxides has been isolated, although Cl_2O_3 may be formed among the oxides of chlorine produced by the action of acids upon potassium chlorate (p. 79). No representatives of this group of compounds are of pharmaceutical interest.

MONOHYDROXIDES OF THE HALOGENS

With X as the general symbol for the halogens acting in their monovalent state, the following monohydroxides and their dehydration products, together with the names, are indicated as follows:

X—OH	X_2O
MONOHYDROXIDE ("HYPO-OUS" ACID)	MONOXIDE ("HYPO-OUS" ACID ANHYDRIDE)
Cl—OH	Cl_2O
* Hypochlorous acid	Chlorine monoxide (Hypochlorous acid anhydride)
Br—OH	Br_2O
Hypobromous acid	Bromine monoxide (Hypobromous acid anhydride)
I—OH	I_2O
Hypoiodous acid	Iodine monoxide (Hypoiodous acid anhydride)

* Compounds that are of pharmaceutical importance and are represented in the U.S.P. or N.F., either as such or in the form of their salts.

Halogen monohydroxides, the "hypo-ous" acids, are obtained in solution by the action of dilute acids upon their salts, the metallic hypohalites. The acids are not known in the anhydrous state and exist only in aqueous solution and in the form of their salts.

Hypochlorous acid is represented as its sodium salt in the U.S.P. Sodium Hypochlorite Solution and Sodium Hypochlorite Test Solution and in the N.F. Diluted Sodium Hypochlorite Solution. There was formerly official a stronger Solution of Chlorinated Soda (Labarraque's Solution) in the U.S.P. X and a Solution of Chlorinated Potassa (Javelle Water) in the N.F. IV. Hypochlorous acid is also represented in the U.S.P. XIII Chlorinated Lime (Bleaching Powder), probably chiefly as a mixed salt of calcium chloride hypochlorite, CaCl(OCl). Besides these official preparations, hypochlorous acid is contained in the form of its salts in numerous nonofficial hypochlorite powders and solutions available on the market for bleaching and disinfectant purposes.*

Hypobromous acid is represented as its sodium salt in the U.S.P. Sodium Hypobromite Test Solution and is also formed in the mixing of the N.F. Hypobromite Reagent for urea estimation (p. 30). Hypoiodous acid is formed as its ammonium salt, ammonium hypoiodite, when iodine is decolorized by the action of ammonia in the preparation of the N.F. Iodides Tincture.

Methods of Formation and Preparation. Methods of formation and preparation of the hypo-ous acids will be considered first.

I. ACTION OF WATER (HYDRATION) ON HALOGEN MONOXIDE. When chlorine monoxide, the only halogen monoxide commonly known (formed by the action of chlorine on mercuric oxide), is dissolved in water, hypochlorous acid is formed:

$$Cl_2O + H_2O \rightarrow 2Cl\text{—}OH$$

II. ACTION OF WATER (HYDROLYSIS) ON HALOGEN. It has been shown previously (p. 39) that chlorine reacts with water with the formation of hydrochloric acid and oxygen. Actually, however, there is evidence to show that probably the chlorine is first hydrolyzed to a mixture of hydrochloric and hypochlorous acids,

$$Cl_2 + HOH \rightarrow HCl + HOCl$$

the hypochlorous acid then liberating oxygen in a subsequent reaction. Thus, absolutely dry chlorine will exert no bleaching action itself but in the presence of moisture it will act as a strong bleaching agent, due to the presence of hypochlorous acid formed as shown above.

III. ACTION OF AN ACID UPON A METALLIC HYPOHALITE.

$$M'OX + H^+ \rightarrow M^+ + X\text{—}OH$$

A. $NaOCl + HOOCCH_3 \rightarrow CH_3COONa + HOCl$

This reaction takes place in the test for identity and in the assay of the U.S.P. Sodium Hypochlorite Solution and the N.F. Diluted Sodium Hypochlorite Solution. The reaction does not stop here, however. Hydrochloric acid, which is formed from the

* As a class project, students may be asked to visit local drug, grocery and dairy supplies stores and list the names and descriptions of the various hypochlorite preparations found on the shelves.

sodium chloride present in the solution, then interacts with the hypochlorous acid to liberate chlorine (p. 29):

$$HCl + HOCl \rightarrow H_2O + Cl_2$$

An analogous reaction takes place when Diluted Sodium Hypochlorite Solution (Modified Dakin's Solution) is used as an antiseptic for the disinfection of wounds. The acids present in the wound tissue are sufficient to bring about the above reactions; chlorine is liberated or hypochlorous acid, which may alone act as an oxidizing agent, is produced and the organisms which cause infection are destroyed.

B. $$Ca\begin{matrix}\diagup Cl \\ \diagdown OCl\end{matrix} + 2HOOCCH_3 \rightarrow$$

$$(CH_3COO)_2Ca + HCl + HOCl$$

This reaction takes place in the assay of the U.S.P. Chlorinated Lime for "available chlorine." Again, as in the preceding example, chlorine is liberated by further interaction of the hydrochloric and hypochlorous acids.

When Chlorinated Lime is used for bleaching purposes, water alone or the carbon dioxide of the air is sufficient to bring about the above reactions, with the liberation of chlorine which acts as the bleaching agent, either directly or by reaction with water to liberate oxygen. Even the presence of the pigment to be bleached may induce the reaction.

The same reaction occurs when Bleaching Powder is exposed to the moist atmosphere, as is evidenced by the odor of chlorine given off. Here the carbon dioxide of the air is the acid which liberates the hydrochloric and hypochlorous acids:

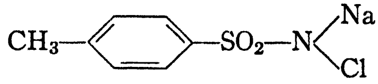
$$Ca\begin{matrix}\diagup Cl \\ \diagdown OCl\end{matrix} + \begin{matrix}HO\diagdown \\ HO\diagup\end{matrix}C{=}O \rightarrow$$

$$CaCO_3 + HCl + HOCl$$

Because of the ease with which this occurs, the U.S.P. contains specific directions for the storage and preservation of Bleaching Powder as well as for the other hypochlorite preparations (p. 30).

IV. Action of Water or an Acid (Hydrolysis) upon a Chloroamide.

$$R{-}N\begin{matrix}\diagup H \\ \diagdown Cl\end{matrix} + HOH \rightarrow RNH_2 + HOCl$$

A. 

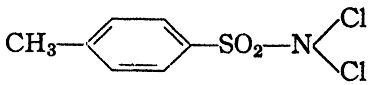
$$+ HOH \rightarrow HOCl$$

It is in this way that the N.F. Chloramine-T exerts its effect as an antiseptic agent, the hypochlorous acid being the oxidizing agent. This reaction occurs even on exposure to moist air, hence the N.F. directs that the product be preserved in well-closed containers.[14] The same reaction is utilized in the assay of the product, the hypochlorous acid reacting further with potassium iodide in presence of acetic acid to liberate iodine which then is titrated with N/10 sodium thiosulfate:

$$HOCl + 2KI + CH_3COOH \rightarrow$$

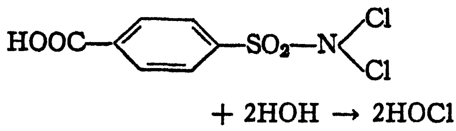
$$KCl + CH_3COOK + H_2O + I_2$$

The term "active chlorine" as used in expressing the strength of such a preparation is confusing and really is a statement of strength in terms of the hypochlorite ion.

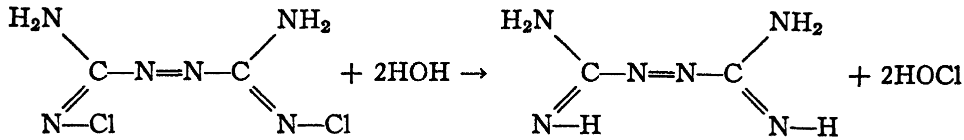
B. 

$$+ 2HOH \rightarrow 2HOCl$$

In the same way, the N.F. Dichloramine-T liberates hypochlorous acid.[15] These two compounds were introduced by Dakin during World War I as disinfecting agents for wounds. Although Dichloramine-T contains much the larger amount of active chlorine, it has the disadvantage of being insoluble in water and must be applied in an oily solution, such as the U.S.P. Eucalyptol or the N.F. Chlorinated Paraffin (Chlorcosane).

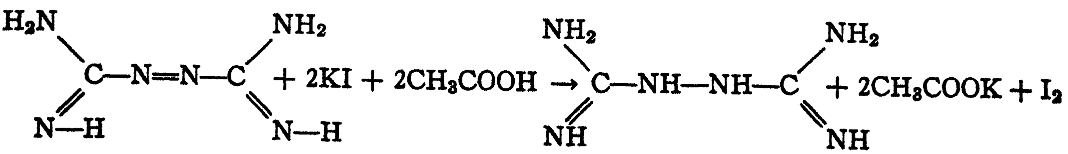
C. 

Halazone N.F., a preparation closely related to Dichloramine-T, is a powerful antiseptic agent, exerting its action by liberation of hypochlorous acid.[16] It is especially useful in the sterilization of drinking water in small quantities and has the added advantage of forming a water-soluble sodium salt.

D. 

The U.S.P. Chloroazodin [17] is one of the more recently introduced organic antiseptics which exerts its action by liberation of hypochlorous acid. It contains a higher percentage of active chlorine than Dichloramine-T, is more stable toward hydrolysis and exerts its antiseptic action over a longer period of time because of its slower liberation of hypochlorous acid. It is commonly used in dilute solution in triacetin, such as the U.S.P. Chloroazodin Solution.

Determination of the active chlorine in Chloroazodin is done as it is for Chloramine-T. In this case, however, due to the structure of Chloroazodin, an additional reaction results in the liberation of more iodine than is accounted for from the hypochlorous acid liberated and this is taken into account in the volumetric factor used. The azo linkage, in being reduced to the hydrazo compound, liberates one mole of iodine:



The hypochlorous acid, released from chloroazodin by hydrolysis, liberates two moles of iodine:

$$2HOCl + 4KI + 2CH_3COOH \rightarrow 2KCl + 2H_2O + 2CH_3COOK + 2I_2$$

The 3 moles of iodine thus liberated are titrated with N/10 sodium thiosulfate:

$$3I_2 + 6Na_2S_2O_3 \rightarrow 6NaI + 3Na_2S_4O_6$$

Methods of Formation and Preparation of the Salts. The methods of formation and preparation of the metallic hypohalites are analogous to those used for preparation of the metallic halates (p. 80).

I. Action of Halogen on Metallic Hydroxide.

$$2M'OH + X_2 \rightarrow H_2O + M'X + M'OX$$

This reaction has already been cited (p. 56). When halogen is added to a solution of alkali, the metallic halide and hypohalite are formed in equal portions. Although the halide may be considered as an impurity, it enters into the liberation of halogen when the hypohalite preparation, made in this way, is assayed or used for bleaching or disinfectant purposes (p. 29).

A. $2NaOH + Cl_2 \rightarrow H_2O + NaCl + NaOCl$

When chlorine is passed into a cold solution of sodium hydroxide, a concentrated "bleach" solution is obtained. Such solutions are used in enormous quantities for the commercial bleaching of paper, cotton and linen goods (p. 35). It is, however, too caustic to be used for medicinal purposes because of the excess of alkali.

B. Many of the sodium hypochlorite solutions sold for use in the household for nonmedicinal bleaching and disinfecting are made according to the above reaction by the electrolysis of a cold brine in cells in which the anode and cathode are not separated by a diaphragm. The electrolytic cell is kept at a low temperature because a higher temperature would lead to further reaction with the formation of sodium chloride and sodium chlorate (p. 81). This method is used extensively where there is an abundant supply of electricity and a source of sodium chloride close at hand.

C. Bleaching Powder, Chlorinated Lime U.S.P., is prepared by passing chlorine over slaked lime. Formerly this product was believed to be a mixture of calcium chloride and calcium hypochlorite. However, calcium chloride is very deliquescent, while bleaching powder is not; calcium chloride is soluble in alcohol, but only traces of calcium chloride can be dissolved out of bleaching powder with alcohol. Finally, all of the chlorine in bleaching powder can be liberated by action of carbonic acid, but if calcium chloride were present, this could not be done. The formula most generally accepted for the main constituent of the product and that which satisfies most of its properties is a mixed calcium chloride-hypochlorite, formed as follows:

$$Ca(OH)_2 + Cl_2 \rightarrow Ca\begin{cases} Cl \\ OCl \end{cases} + H_2O$$

It is probable that bleaching powder is a mixture consisting chiefly of this compound plus some moisture and excess lime. Chlorinated Lime is used in large quantity for bleaching, disinfecting and deodorizing purposes and for the preparation of other hypochlorite preparations and chlorinated products. It has been replaced to some extent in recent years by other hypochlorite preparations containing a higher percentage of available chlorine. One of these, sold under the trade name of Perchloron, is stated to contain 70 per cent of true calcium hypochlorite, $Ca(OCl)_2$, which would yield a considerably higher percentage of "available" chlorine than Chlorinated Lime.

D. $2NaOH + Br_2 \rightarrow H_2O + NaBr + NaOBr$

This is the way in which the U.S.P. Sodium Hypobromite Test Solution is prepared.[18] In the same way, the N.F. Hypobromite Reagent for urea estimation in urine is prepared extemporaneously by mixing a previously prepared solution of bromine and sodium bromide in water with a strong sodium hydroxide solution.[19] Thus, the hypobromite reagent is freshly prepared when needed and no opportunity for oxidation to bromate or for liberation of bromine is afforded.

E. $2NH_4OH + I_2 \rightarrow H_2O + NH_4I + NH_4OI$

When ammonia is added to the iodine-potassium iodide solution in the preparation of the N.F. Iodides Tincture, the above reaction presumably takes place and the solution becomes decolorized.[20]

II. Action of an Alkaline Carbonate on Chlorinated Lime.

A. As stated previously (p. 86), the solution of sodium chloride and sodium hypochlorite prepared by the action of chlorine on sodium hydroxide is too caustic for medicinal purposes because it contains an excess of alkali. A solution, known after its originator as Labarraque's Solution, the Solution of Chlorinated Soda of the U.S.P. X,[21] is prepared by the action of sodium carbonate on Chlorinated Lime:

$$CaCl(OCl) + Na_2CO_3 \rightarrow CaCO_3 + NaCl + NaOCl$$

In this way, a solution of equal proportions of sodium chloride and sodium hypochlorite is obtained; calcium carbonate, being insoluble, is removed by filtration. This solution is not so caustic as the one prepared from

chlorine and sodium hydroxide, its alkalinity being maintained by an excess of sodium carbonate instead of sodium hydroxide. Nevertheless, it was found to be too caustic for irrigating open wounds. In the N.F. Diluted Sodium Hypochlorite Solution,[22] which is used on open wounds, the concentration of chloride and hypochlorite is greatly reduced and the causticity of the preparation is reduced by neutralizing the stronger sodium hydroxide by addition of sodium bicarbonate:

$$NaOH + NaHCO_3 \rightarrow Na_2CO_3 + H_2O$$

A limited amount of alkali in such a preparation is said to be of advantage because of its solvent and destructive action on bacteria and dead tissue, and in this respect, the metallic hypochlorite preparations are preferable to the organic compounds such as Chloramine-T, Chloroazodin, etc. An excess of alkalinity is detrimental because it causes irritation and destruction of normal tissue.

B. A solution prepared by the action of potassium carbonate on Chlorinated Lime was formerly known as Javelle Water, the Solution of Chlorinated Potassa of the N.F. IV:

$$CaCl(OCl) + K_2CO_3 \rightarrow CaCO_3 + KCl + KOCl$$

Since potassium carbonate is even more caustic than sodium carbonate, this preparation had no medicinal value over the less expensive Labarraque's Solution. It has been used to a considerable extent by the housewife for bleaching, removing stains from table linen, clothing, etc.; since it is more stable than the corresponding sodium solution, it may be better suited for bleaching purposes by extending its bleaching and deodorizing activity over a slightly longer period of time.

Properties and Uses. The hypohalous acids are not known in the anhydrous state, but only in dilute aqueous solutions, since they are unstable and readily decompose in higher concentrations. Their stability decreases with an increase in the atomic weight of the halogen; thus, hypochlorous acid is the most stable, hypoiodous acid the least stable. They are acidic in character, although even less strong as acids than carbonic acid, and they form salts. The salts, likewise, with the exception of sodium hypochlorite and calcium hypochlorite, are not known in the solid state but only in aqueous solution because of their instability. The salts are hydrolyzed in solution, even in the presence of an alkali, and in the presence of as weak an acid as carbonic acid, hydrolysis is very rapid.

In some of their properties the hypohalous acids and their salts, the hypohalites, resemble the halic acids and their salts, the halates. Thus, they function as oxidizing agents in two different ways, i.e., directly by the liberation of oxygen, being thereby reduced to halide, and indirectly by the liberation of halogen.

$$\text{I. } HOX \rightarrow HX + \tfrac{1}{2}O_2$$
$$M'OX \rightarrow M'X + \tfrac{1}{2}O_2$$

Hypochlorous acid readily loses its oxygen and changes into hydrochloric acid. This decomposition is accelerated by the presence of free acid and sunlight. In the same way, the metallic hypochlorites readily part with their oxygen, and it is in this way that Chlorinated Lime and the other hypochlorite preparations act directly as oxidizing, bleaching and disinfectant agents, the oxygen thus liberated being the actual bleaching and disinfectant agent. This is also one cause of deterioration of such products, and for that reason, hypochlorite preparations are directed to be protected from light during storage.

$$\text{II. } HOX + HX \rightarrow H_2O + X_2$$
$$M'OX + M'X \xrightarrow{(2H^+)} 2M^+ + H_2O + X_2$$

As mentioned previously (p. 29), it is in this way that hypochlorous acid and the hypochlorites liberate chlorine, by reaction with a hydrogen halide. These reactions are

involved not only in the test for identity and assay of the U.S.P. and N.F. hypochlorite preparations, but also in the use of such preparations as oxidizing and bleaching agents. Undoubtedly this reaction also occurs subsequent to the one given above, the hydrogen chloride being furnished by direct liberation of oxygen from hypochlorous acid, so that oxygen and chlorine are liberated simultaneously. The chlorine thus liberated may act directly as the bleaching or disinfectant agent or through its reaction with water to liberate oxygen:

$$Cl_2 + H_2O \rightarrow 2HCl + \tfrac{1}{2}O_2$$

or

$$Cl_2 + H_2O \rightarrow HCl + HOCl$$

$$HOCl \rightarrow HCl + \tfrac{1}{2}O_2$$

These reactions help to explain the deteriorating action of light on Chlorine Water (p. 39). Even the moisture and carbon dioxide of the atmosphere are sufficient to hydrolyze the salts and allow the reaction to take place.

When a hypohalous acid or a metallic hypohalite in solution is heated, it is changed into halate and halide (p. 56):

$$3HOX \rightarrow HO_3X + 2HX$$

$$3M'OX \rightarrow M'O_3X + 2M'X$$

In this case the bleaching and oxidizing power of the hypohalite is destroyed by heating, hence the U.S.P. and N.F. directions that the hypochlorite preparations be stored in a cool place. This decomposition is accelerated by a higher concentration of hypohalite, but in the case of metallic hypochlorites, it is almost completely inhibited by the presence of excess alkali. Hence, bleaching powder to be used or stored in hot climates usually contains an added excess of slaked lime for preservation.

In summary, hypochlorite solutions and powders are used for disinfecting, deodorizing and bleaching since, being good oxidizing agents, they destroy organic coloring matter and the organisms which promote infection and decay. As chemical reagents, a solution of sodium or calcium hypochlorite is used to distinguish between arsenic and antimony, the metallic mirror produced on porcelain by the reduction of arsenic compounds in the Marsh test being readily soluble in hypochlorite, while a similar mirror produced from antimony is insoluble in this reagent (p. 149). They also are used in large quantity as oxidizing and chlorinating agents in the preparation of other chemicals.

REFERENCES

1. N.F. VIII, p. 406, under Identification test A.
2. U.S.P. XIII, p. 428.
3. *Ibid.*, p. 861.
4. N.F. VIII, p. 406, Identification test B.
5. See method of preparation and definition of Compound Solution of Chlorine, N.F. V, p. 127.
6. Note Caution under identification test for Chlorate, U.S.P. XIII, p. 659.
7. N.F. VIII, p. 303, under test for Bromate.
8. U.S.P. XIII, p. 427, under test for Iodate.
9. *Ibid.*, p. 804, under test for Iodide.
10. N.F. VIII, p. 406.
11. U.S.P. XI, p. 164.
12. U.S.P. XIII, p. 799.
13. *Ibid.*, p. 659.
14. N.F. VIII, p. 141.
15. *Ibid.*, p. 181.
16. *Ibid.*, p. 245.
17. U.S.P. XIII, p. 123.
18. *Ibid.*, p. 843.
19. N.F. VIII, p. 605.
20. *Ibid.*, p. 261.
21. U.S.P. X, p. 224.
22. N.F. VIII, p. 483.

6

Elements of Group VI

ELEMENTS—THE OXYGEN OR SULFUR SUBGROUP

The elements included in this subgroup are oxygen, sulfur, selenium and tellurium. The latter three elements formed one of Döbereiner's "triads," a forerunner of the modern periodic system of elements (p. 7). Although oxygen is grouped with the other three elements here, it differs considerably in certain of its chemical properties. Thus, whereas all of the elements exhibit toward hydrogen or other electropositive elements or groups a negative character and a valence of two, toward oxygen or other electronegative elements or groups sulfur, selenium and tellurium exhibit a positive character and most commonly valences of four or six. No ordinary compounds in which oxygen may be considered as having a positive character are known. Oxygen and sulfur are distinctly nonmetallic, while selenium and tellurium show some metallic properties. Another characteristic of the group is the existence of allotropic forms of the elements.

History. Oxygen, although of universal distribution because it is a gas, escaped notice as a particular substance until near the close of the eighteenth century. The four elements of the ancient world were air, earth, fire and water, and it was believed that the air was a simple or elementary substance. The investigations of Priestley, Rutherford and Scheele, however, showed distinctly that air is a mixture of at least two different gases, only one of which is capable of supporting combustion and respiration. This constituent is oxygen, which was discovered by Priestley (p. 37) in England on August 1, 1774, while heating red mercuric oxide (mercury calx). He regarded the new gas as "dephlogisticated air," while he designated as "phlogisticated air" that portion of the atmosphere which remained after combustion and which supported neither combustion nor respiration, namely, nitrogen. Priestley also named the new gas "life air" because he observed that it supported the respiration of a mouse.

At least a year before Priestley's announcement, Scheele (p. 20) had discovered oxygen, independently of Priestley, but did not publish his results immediately.[1] Scheele had observed its formation by heating pyrolusite with sulfuric acid, and also by heating nitrates and by heating the oxides of silver and mercury. He called the new gas "fire air" because it supported burning and combustion. According to Scheele this "fire air" and phlogiston (p. 20) were the components of heat. He regarded that component of the atmosphere which supported neither respiration nor combustion, i.e., the nitrogen, as "spent air" or vitiated air. Oxygen had been prepared by others several times before this date but it remained for Scheele to recognize its peculiarities.

The discovery of oxygen enabled Lavoisier

(p. 38) to expound the true theory of combustion. Because of the acidic nature of some of the products of combustion and because he believed this new gas to be responsible for the acidic properties of many substances, Lavoisier gave it the name "oxygene," meaning acid-former (literally, "to produce sour"). Although this name has remained, it is an unfortunate misnomer since oxygen is also the constituent of the hydroxides and oxides of the metals which gives to these substances their basic character.

As early as 1785, Van Marum, a Dutch chemist, reported the observation that the passage of an electric spark through oxygen or air produced a peculiar odor and that the modified oxygen was capable of tarnishing mercury. It was not until 1840, however, that Schoenbein, a German chemist, drew attention to other properties and to the methods of formation of this odorous gas and gave to it the name ozone (I smell). It was recognized as an allotropic form of oxygen, and Andrews, in 1856, established the fact that it is the same substance no matter what the source.

Sulfur was one of the earliest known elements and was used by the ancient peoples as a medicament and fumigant. It played an important role in the iatrochemical (medicochemical) school of Paracelsus in the sixteenth century (p. 7). Sulfur was known in the free or native state and in combinations. It was formerly called brimstone (*Brennestein*, burning stone) and was considered by the alchemists to be one of the principles of combustion or phlogiston. They believed it to play a role in the alteration of metals when the latter were burned. It was not until the nineteenth century that Mitscherlich discovered the dimorphism of sulfur, i.e., its property to exist in two different crystalline forms, rhombic and monoclinic.

Selenium and tellurium were discovered at much later dates. A native form of tellurium was examined in 1782 by von Reichenstein, who concluded that it contained a peculiar metal. At his suggestion Klaproth,* in 1798, investigated several tellurium ores, confirmed the former's views and named the new metallic element tellurium (from tellus, the earth). Berzelius later examined the element more closely, and because of its properties, analogous to those of sulfur and selenium, it was placed in the sulfur group of elements.

Selenium was discovered in 1817 by Berzelius in the lead chambers used in the production of sulfuric acid at Gripsholm, Sweden. It was named after the Greek word for the moon because of its analogy to tellurium (the earth), discovered shortly before.

Occurrence. Oxygen is the most abundant of all the elements on our planet, making up more than 50 per cent of the earth and its atmosphere. It occurs in the free state throughout the atmosphere, constituting about 20 per cent of this part of the earth, and without it animal life would be impossible. The chief mass of the earth's crust consists of rocks containing silicates, carbonates and other compounds of various metals and nonmetals with oxygen; these rocks contain 40 to 50 per cent of oxygen. In the form of its dihydride, H_2O, oxygen is as universal as it is in the free state, occurring in this combination in the solid phase (ice), the liquid phase (water) and the vapor phase (moisture of the air).

Sulfur also occurs extensively as the free element and in chemical combinations, organic as well as inorganic. Free sulfur is found in all of the volcanic regions of the world, the most important of which are in Sicily, Italy, Chile, Peru, Utah, Colorado,

* Martin Heinrich Klaproth (1743-1817), a German apothecary-chemist, the first professor of chemistry in the University of Berlin, is considered the father of modern analytical chemistry. He is best known for his researches in mineralogic chemistry, most of which were carried out in his own pharmacy; he first recognized the elementary character of uranium, titanium, zirconium, strontium and cerium, among others.

Wyoming and other western states in the United States. The regions of Italy and Sicily were at one time the chief sources of the sulfur of commerce, but extensive deposits of very pure sulfur found in the south and southwestern United States, especially Louisiana and Texas, and obtained by the Frasch process, now supply all of the requirements of this country and provide much of the world's supply.

The explanations of sulfur formation and deposition in volcanic regions vary. One such belief is that sulfur dioxide and hydrogen sulfide, contained in volcanic gases, upon coming in contact, react with each other to form free sulfur by mutual oxidation-reduction:

$$SO_2 + 2H_2S \rightarrow 3S + 2H_2O$$

Other explanations are that such deposits are formed by deposition from sulfur-bearing waters or by the reducing action of organic agencies, such as micro-organisms, on gypsum, $CaSO_4 \cdot 2H_2O$.

In inorganic combination, in the form of sulfides and sulfates, sulfur is widely distributed throughout the earth's surface. The most important of these are:

SULFIDES

FeS_2, Iron Pyrites
$CuFeS_2$, Copper Pyrites
PbS, Galena
HgS, Cinnabar
ZnS, Zinc Blend

SULFATES

$CaSO_4 \cdot 2H_2O$, Gypsum
$BaSO_4$, Barytes
$MgSO_4 \cdot XH_2O$, Kieserite
$Na_2SO_4 \cdot 10H_2O$, Glauber's Salt
$FeSO_4 \cdot 7H_2O$, Green Vitriol

Sulfur occurs in organic combination in the plant and animal kingdoms in proteins, hair, wool, volatile oils and many other products elaborated by these organisms. Selenium and tellurium are found in very small amounts in the free state, but more generally are found in inorganic combination. Selenium usually is found associated with sulfur in the free state and in ores. This was responsible for its discovery in the lead chambers used in the production of sulfuric acid. The analogy existing among sulfur, selenium and tellurium is indicated in the naturally occurring lead compounds of these elements, all of which crystallize in the same regular system: PbS, PbSe and PbTe.

Methods of Formation and Preparation. The value of any science lies in the generalizations that may be made from specific facts and in the deductions as to specific cases that may be applied from these generalizations. Likewise, in the presentation and study of a science such as chemistry, the student may well be impressed with the importance of grasping the generalizations that are present and apparent to aid him in his study of the subject matter. It is with this thought in mind that the methods of formation and preparation of the elements of the sixth group are presented along the same general lines as those followed under the halogens. The similarity and analogy between the two groups will become apparent upon a comparison of these two sections.

I. DISSOCIATION OF THE SIMPLE HYDRIDES.

A. $2H_2O \xrightarrow{\text{energy}} 2H_2 + O_2$

Very high temperature is necessary to bring about this dissociation. Water can also be dissociated by an electric current; pure water is electrolyzed only with difficulty, but if an electrolyte is present, the electrolysis takes place more easily. Oxygen for industrial and medicinal purposes has been prepared by this process on a commercial scale, with hydrogen as a by-product, but it cannot compete with the large-scale manu-

facture of oxygen from liquid air by fractional distillation.

B. $H_2S \xrightarrow{\text{energy}} H_2 + S$

This reaction takes place at a much lower temperature than the dissociation of water. It can be brought about by passing a current of H_2S through a red-hot tube.

II. Dissociation of Metallic "-ides" (Oxides, Sulfides, Etc.). Both Priestley and Scheele discovered oxygen by heating red mercuric oxide:

$$2HgO \xrightarrow{\text{energy}} 2Hg + O_2$$

The oxides of the noble metals are dissociated at relatively low temperatures. This reaction is made use of in a test for purity of the N.F. Red Mercuric Oxide.[2]

III. Breaking Down of a Higher "-ide" to Lower "-ide" and the Element. Elements, both metallic and nonmetallic, which form higher oxides and sulfides give off part of their oxygen or sulfur when heated and are converted into a lower oxide or sulfide.

A. $2H_2O_2 \rightarrow 2H_2O + O_2$

This reaction occurs slowly at ordinary temperatures but is accelerated by heat and light, hence the U.S.P. directs that Hydrogen Peroxide Solution be preserved in a cool place protected from light.[3]

B. $3MnO_2 \xrightarrow{\Delta} Mn_3O_4 + O_2$

Manganese dioxide liberates oxygen at a rather high temperature, and this reaction has been used as a test for its identity[4] as well as for the preparation of small amounts of oxygen.

C. $2BaO_2 \xrightarrow{\Delta} 2BaO + O_2$

Barium dioxide is particularly suitable for the production of oxygen and this was at one time a commercial method used in the now obsolete Brin process. The barium peroxide liberates oxygen at a temperature of approximately 800° C., and the barium oxide so obtained is reoxidized to the dioxide at approximately 500° C.

D. $H_2S_5 \xrightarrow{\Delta} H_2S + 4S$

This reaction may take place in the preparation of the U.S.P. Precipitated Sulfur, concerning which more will be said later (p. 94). Upon boiling sulfur with slaked lime, calcium pentasulfide, CaS_5, among other products, is formed; when this is treated with hydrochloric acid, hydrogen pentasulfide is formed, and breaks down as shown above.

E. $FeS_2 \xrightarrow{\Delta} FeS + S$

This reaction occurs in the preparation of sulfur from pyrites by roasting the ore under carefully controlled conditions. When carried out in the presence of excess oxygen, the pyrites is oxidized to Fe_2O_3 and SO_2.

IV. Action of Heat on Salts Rich in Oxygen ("-ate" Compounds).

A. $2KClO_3 \xrightarrow{\Delta} 2KCl + 3O_2$

$4KClO_3 \xrightarrow{\Delta} KCl + 3KClO_4$

$3KClO_4 \xrightarrow{\Delta} 3KCl + 6O_2$

These reactions, discussed previously (pp. 58, 82), are used as test for identity of Potassium Chlorate and also as one of the common laboratory methods for the preparation of oxygen. A catalyst of manganese dioxide causes the liberation of oxygen more smoothly and at a lower temperature and the MnO_2 may be recovered unchanged from the process.

B. $2KNO_3 \xrightarrow{\Delta} 2KNO_2 + O_2$

This reaction was used by Scheele in one of his methods of preparation of oxygen and has also been used as a test for identity of potassium nitrate.[5]

C. $2KMnO_4 \xrightarrow{\Delta} K_2MnO_4 + MnO_2 + O_2$

This reaction has been referred to previously (p. 76); it has also been used as a

test for identity of potassium permanganate.[6]

V. Action of Suitable Acid on Higher "-ides" (Oxides, Sulfides, Etc.).

A. $2MnO_2 + 2H_2SO_4 \rightarrow$

$$2MnSO_4 + 2H_2O + O_2$$

This reaction is of historical interest as one of the experiments which Scheele carried out to prepare oxygen and has also been used as a test for identity of manganese dioxide. If hydrochloric acid is used, chlorine, rather than oxygen, is evolved (p. 24):

$$MnO_2 + 4HCl \rightarrow MnCl_2 + 2H_2O + Cl_2$$

When, however, a mixture of two moles of barium peroxide and one mole of manganese dioxide is treated with hydrochloric acid, oxygen is generated as follows:

$$4BaO_2 + 2MnO_2 + 12HCl \rightarrow$$

$$4BaCl_2 + 2MnCl_2 + 6H_2O + 3O_2$$

Before the advent of the modern oxygen tank, this method was made use of in an oxygen generator for the administration of oxygen in artificial respiration.

B. In a similar manner, chromium trioxide when treated with hydrochloric acid yields chlorine:

$$2CrO_3 + 12HCl \rightarrow 2CrCl_3 + 6H_2O + 3Cl_2$$

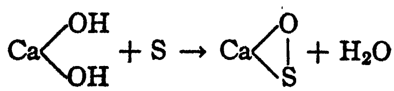
When treated with sulfuric acid it yields oxygen:

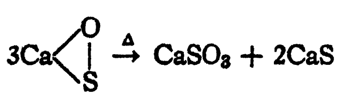
$$4CrO_3 + 6H_2SO_4 \rightarrow$$

$$2Cr_2(SO_4)_3 + 6H_2O + 3O_2$$

C. $CaS_5 + 2HCl \rightarrow ClCl_2 + H_2S + 4S$

This reaction occurs in the preparation of U.S.P. Precipitated Sulfur as it is commonly prepared.[7] Sulfur is first boiled with an aqueous mixture of slaked lime; the following reactions take place:





yielding calcium sulfide and calcium sulfite. When boiled in the presence of excess sulfur, these products further react as follows:

$$CaSO_3 + S \xrightarrow{\Delta} CaS_2O_3$$

$$CaS + S \xrightarrow{\Delta} CaS_2$$

$$CaS_2 + S \xrightarrow{\Delta} CaS_3$$

$$CaS_3 + S \xrightarrow{\Delta} CaS_4$$

$$CaS_4 + S \xrightarrow{\Delta} CaS_5$$

They yield a solution of calcium thiosulfate and the higher sulfides of calcium, chiefly calcium pentasulfide, CaS_5, when proper conditions are observed. The sum total of the above reactions is usually written in one, as follows:

$$3Ca(OH)_2 + 12S \rightarrow$$

$$2CaS_5 + CaS_2O_3 + 3H_2O$$

When the solution resulting from the above reactions is treated with hydrochloric acid, as directed by the U.S.P. X, a reaction takes place between the polysulfides of calcium and the acid, forming $CaCl_2$ (soluble), H_2S (gas) and free S (insoluble). In this way a pure, finely divided form of sulfur is obtained. When hydrochloric acid is added only until the solution is nearly, but not entirely, neutralized, and still retains an alkaline reaction and a pale yellow color, as directed, the precipitation stops here. If, however, hydrochloric acid is added until the solution is acid in character, it loses its color and more sulfur is precipitated, this time from the calcium thiosulfate (p. 144):

$$CaS_2O_3 + 2HCl \rightarrow$$

$$CaCl_2 + SO_2 + H_2O + S$$

The sulfur thus precipitated from the calcium thiosulfate, instead of coming down in a finely divided form which dries into an almost impalpable powder, such as is desired, forms instead a somewhat gelatinous precipitate which agglutinates in a sticky mass and dries in undesirable hard lumps. Nor does the reaction necessarily stop at

this point. The sulfur dioxide and hydrogen sulfide in solution may react:

$$SO_2 + 2H_2S \rightarrow 2H_2O + 3S$$

thus yielding still more sulfur.

There is still another reason for stopping the addition of hydrochloric acid before the solution becomes acid in reaction. In former years sublimed sulfur, which is used in the preparation of Precipitated Sulfur, very frequently contained a small amount of arsenic impurity in the form of sublimable arsenic trisulfide. When boiled with slaked lime, the arsenic trisulfide forms soluble calcium orthoarsenite, $Ca_2(AsO_3)_2$, and calcium orthothioarsenite, $Ca_3(AsS_8)_2$ (p. 199):

$$2As_2S_3 + 6Ca(OH)_2 \rightarrow Ca_3(AsO_3)_2 + Ca_3(AsS_3)_2 + 6H_2O$$

It is possible that calcium orthothioarsenite is formed also by reaction of the arsenic trisulfide with the calcium sulfide:

$$As_2S_3 + 3CaS \rightarrow Ca_3(AsS_3)_2$$

The calcium orthoarsenite and orthothioarsenite remain in solution as long as the liquid is alkaline. If it is made acid, however, these soluble arsenic compounds are decomposed again into insoluble arsenic trisulfide and arsenic trioxide which will again contaminate the precipitated sulfur:

$$Ca_3(AsS_3)_2 + 6HCl \rightarrow 3CaCl_2 + As_2S_3 + 3H_2S$$

$$Ca_3(AsO_3)_2 + 6HCl \rightarrow 3CaCl_2 + As_2O_3 + 3H_2O$$

For this reason, the U.S.P. directs a test for arsenic impurity in Precipitated Sulfur.[8]

It should be noted that hydrochloric acid is specified for precipitating the sulfur in this preparation. If sulfuric acid were used in place of hydrochloric acid, insoluble calcium sulfate would be precipitated along with the sulfur to yield a product which is contaminated with calcium sulfate. This practice was indulged in years ago by unscrupulous manufacturers, and samples of this product obtained from various sources have yielded as high as 40 per cent and more of ash, showing the presence of large quantities of calcium sulfate. The Pharmacopœia discouraged this practice by the simple expedient of including a limit of residue on ignition, the present revision allowing not more than 0.3 per cent residue.[8]

VI. Action of a Suitable Acid on Salts Rich in Oxygen (Oxidizing Agents).

A. In method V-B, above, it was shown that chromium trioxide yields oxygen when treated with sulfuric acid. In a similar way, potassium dichromate, when it is used as a quantitative oxidizing agent in the presence of sulfuric acid, *acts as though* it liberates oxygen as follows:

$$K_2Cr_2O_7 + 4H_2SO_4 \rightarrow K_2SO_4 + Cr_2(SO_4)_2 + 4H_2O + 3O$$

From this it may be seen that the gram equivalent weight of $K_2Cr_2O_7$ (the amount equivalent to 8.000 Gm. of oxygen) is $\frac{1}{6}$ of its gram molecular weight, or $K_2Cr_2O_7/6$. For each mole of potassium dichromate used *it may be considered* that three atoms of oxygen are available for oxidizing purposes and that they will oxidize six equivalent weights of a reducing agent. This method of considering and of balancing oxidation-reduction equations involving dichromate is sometimes less confusing than methods which use gain or loss in electrons or change in valence.

Potassium dichromate formerly was used in the assay of the ferrous carbonate preparations (Mass, Pills and Saccharated Ferrous Carbonate) of the present N.F., but it has since been replaced by a ceric sulfate titration (p. 210). However, the dichromate method still is employed extensively in the assay of industrial iron products, iron ore, etc. The N.F. VI assay of Saccharated Ferrous Carbonate[9] will serve to illustrate the reactions involved. The weighed sample is dissolved in diluted sulfuric acid and titrated with N/10 potassium dichromate:

$$6FeCO_3 + K_2Cr_2O_7 + 13H_2SO_4 \rightarrow K_2SO_4 + Cr_2(SO_4)_3 + 3Fe_2(SO_4)_3 + 6CO_2 + 13H_2O$$

The amount of ferrous carbonate in the sample is thus expressed in terms of the amount of N/10 potassium dichromate required to oxidize it.

B. The way in which potassium permanganate *may be considered* to make available oxygen, when it is used as a quantitative oxidizing agent in the presence of sulfuric acid, has been discussed (p. 77). A similar approach may be used in the balancing of oxidation-reduction equations involving permanganate.

Since both potassium permanganate and potassium dichromate are highly colored compounds and give characteristically colored solutions, their oxidizing action is accompanied by changes in color. This color change is especially useful in the case of permanganate, where colorless compounds result, thus obviating the necessity for an indicator. With dichromate, however, the color change is not so definite since one of the products of the reaction, chromic sulfate, is also colored; an indicator is necessary when this reagent is used.

The oxidizing property of potassium permanganate is illustrated innumerable times in the U.S.P. and N.F. in various tests for identity and purity and in assays. A representative number of these are cited here to show its extensive use. Among tests in which it is employed are those for lactates; [10] among tests for impurity are those for Acetone,[11] Acetic Acid,[12] Alcohol,[13] Ammonia Water,[14] Cocaine [15] and many others.

The variety of ways in which potassium permanganate is used as a quantitative oxidizing agent in U.S.P. and N.F. assays is illustrated in the following list:

1. Oxidation of ferrous to ferric iron: The U.S.P. and N.F. have adopted the ceric sulfate method for the assay of those ferrous iron preparations which contain, in addition to the ferrous compound, organic substances which might also be oxidized by permanganate; but the U.S.P. still uses the permanganate method for Ferrous Sulfate.[16] In this assay the weighed sample is dissolved in diluted sulfuric acid and titrated with N/10 potassium permanganate:

$$10FeSO_4 + 2KMnO_4 + 8H_2SO_4 \rightarrow 5Fe_2(SO_4)_3 + K_2SO_4 + 2MnSO_4 + 8H_2O$$

The amount of ferrous sulfate in the sample is thus expressed in terms of the amount of N/10 potassium permanganate required to oxidize it.

In the U.S.P. assay of Potassium Chlorate, Reagent,[17] the weighed sample is allowed to oxidize all that it is capable of oxidizing of a measured excess of ferrous sulfate test solution:

$$6FeSO_4 + KClO_3 + 3H_2SO_4 \rightarrow 3Fe_2(SO_4)_3 + KCl + 3H_2O$$

The excess of ferrous sulfate test solution remaining after this oxidation then is titrated with N/10 permanganate, and the amount of potassium chlorate in the sample is calculated in terms of the amount of N/10 permanganate to which it is equivalent. By inspection of the reactions of ferrous sulfate with potassium permanganate and with potassium chlorate, respectively, it may be seen that 1 gram mole $KMnO_4$ is equivalent to $\frac{5}{6}$ gram mole $KClO_3$.

2. Oxidation of oxalic acid to carbon dioxide and water: This reaction is utilized in the assay of the U.S.P. Potassium Permanganate,[18] in the standardization of both Oxalic Acid, Tenth-Normal [19] and of Potassium Permanganate, Tenth-Normal,[20] in the assay of the N.F. Manganese Dioxide [21] and in the assays of calcium and lead in many of their compounds in the U.S.P. and N.F.

In the assay of Potassium Permanganate,[18] as an example, there is added to the weighed sample a measured excess of N/10 oxalic acid and the excess then is determined by titration with N/10 potassium permanganate:

$$2KMnO_4 + 5H_2C_2O_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 10CO_2 + 8H_2O$$

The amount of $KMnO_4$ in the sample is then expressed in terms of the amount of N/10 oxalic acid to which it is equivalent.

The standardization of the U.S.P. volumetric solutions of Potassium Permanganate [20] and Oxalic Acid [19] involve the same reactions and equivalences. In the assay of Manganese Dioxide,[21] part of a measured excess of N/10 oxalic acid is oxidized to carbon dioxide and water by the weighed sample of manganese dioxide and the excess of oxalic acid then is determined by titration with N/10 permanganate.

In the assay of the lead content of the N.F. Lead Subacetate Solution,[22] for example, a measured excess of N/10 oxalic acid is added to the measured sample, with the precipitation of insoluble lead oxalate. The amount of excess oxalic acid in the filtrate is determined by titration with N/10 permanganate.

In the assay of the N.F. Calcium Bromide,[23] insoluble calcium oxalate is precipitated by the addition of ammonium oxalate to the weighed sample. This precipitate is collected on a filter, washed free of soluble oxalate and then converted, by action of sulfuric acid, to free oxalic acid. The latter is then titrated with N/10 permanganate:

$$5CaBr_2 + 5(NH_4)_2C_2O_4 \rightarrow 10NH_4Br + 5CaC_2O_4$$

$$5CaC_2O_4 + 5H_2SO_4 \rightarrow 5CaSO_4 + 5H_2C_2O_4$$

$$2KMnO_4 + 5H_2C_2O_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 10CO_2 + 8H_2O$$

The amount of calcium bromide in the sample is expressed in terms of the amount of N/10 permanganate to which it is equivalent.

The assays of almost all of the other calcium compounds of the U.S.P. and N.F. are based on analogous reactions and chemical equivalences and differ only in the details of precipitation and filtration of the calcium oxalate.

3. Oxidation of hydrogen peroxide to water and oxygen: This reaction is utilized in the assays of the U.S.P. Hydrogen Peroxide Solution [24] and Sodium Perborate,[25] as well as other preparations containing or yielding hydrogen peroxide. In the case of Sodium Perborate, hydrogen peroxide is produced by its reaction with water (p. 108); in the assay of Hydrogen Peroxide Solution, the measured sample is titrated directly with N/10 permanganate in the presence of sulfuric acid. The hydrogen peroxide, in liberating oxygen, may be said to be acting as a reducing agent and is oxidized by the permanganate, the oxygen from which forms molecular oxygen with that contributed by the peroxide:

$$2KMnO_4 + 5H_2O_2 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 8H_2O + 5O_2$$

4. Oxidation of nitrite to nitrate: This reaction is utilized in the assay of the U.S.P. Sodium Nitrite [26] and Potassium Nitrite, Reagent. In the former, a solution of the weighed sample is added to a measured excess of N/10 permanganate in the presence of sulfuric acid and the oxidation is allowed to proceed:

$$4KMnO_4 + 10NaNO_2 + 11H_2SO_4 \rightarrow 5Na_2SO_4 + 2K_2SO_4 + 4MnSO_4 + 10HNO_3 + 6H_2O$$

The excess permanganate then is determined by a residual titration procedure and the amount of sodium nitrite in the sample is expressed in terms of the amount of N/10 permanganate to which it is equivalent.

5. Oxidation of iodide to iodate: This reaction, which has been referred to previously (p. 32), is used in the assay of iodine in Thymol Iodide and in certain other organic iodine compounds. In this case, however, where potassium permanganate acts as

an oxidizing agent in alkaline solution, the reaction takes a different course.

VII. REPLACEMENT IN AN "-IDE" OF ELEMENT OF HIGHER ATOMIC WEIGHT BY ELEMENT OF LOWER ATOMIC WEIGHT IN GROUP VI. Since oxygen is the element of this group with the lowest atomic weight, it is obvious that oxygen cannot be formed by this method. Hence the method, which is an oxidation reaction, applies only to the other members of this group. Since selenium and tellurium and their compounds are of little pharmaceutical importance, this method is of pharmaceutical interest chiefly in its application to the formation of sulfur.

A. 1. H_2S gas $+ \frac{1}{2}O_2 \rightarrow$

H_2O gas $+ S + 55.6$ Cal.

2. H_2S aq. $+ \frac{1}{2}O_2 \rightarrow$

H_2O liq. $+ S + 61.8$ Cal.

This reaction, as the thermochemical equation indicates, is strongly exothermic and takes place readily. For this reason Hydrogen Sulfide T.S. of the U.S.P. is unstable in storage and decomposes on exposure to air, the decomposition taking place more rapidly in presence of heat and light. This explains why the U.S.P. directs that this reagent be kept in small, amber-colored bottles, filled nearly to the top and stored in a cool, dark place.[27]

A practical application is made of this reaction in the aeration of cisterns in order to remove foul odors from rain water. Hydrogen sulfide in the air, resulting from incomplete combustion of coal and coal gas and from the decay of organic matter, collects on roofs, is dissolved in the rain water and washed into cisterns, where it accumulates and imparts a bad odor to the water. By aeration, i.e., stirring up the water so that air may come in contact with all parts of it, the hydrogen sulfide is oxidized, the bad odor disappears and the sulfur which is formed settles to the bottom of the cistern. The same result can be brought about more easily and quickly by dissolving a few grams of potassium permanganate in water and adding the solution to the water in the cistern. It is necessary, after this treatment, to wait several hours before using the water in order to allow time for the brown oxides of manganese to settle out.

B. An analogous reaction takes place when oxygen is allowed to come into contact with a metallic sulfide. This accounts, in part, for the changes which occur in the N.F. Sulfurated Potash (p. 127) when it is exposed to the air, and explains the N.F. directions for storing this product in airtight containers.[28]

C. $Na_2S_2O_3$ aq. $+ \frac{1}{2}O_2 \rightarrow$

Na_2SO_4 aq. $+ S + 70$ Cal.

This somewhat similar reaction occurs when sodium thiosulfate, either in the solid state or in solution, is exposed to the air; this reaction is one of the reasons why this chemical (p. 144) is unstable in storage. It also helps to explain why sodium thiosulfate, which is a valuable reagent for the determination of iodine, cannot be used for the determination of chlorine or bromine directly; it is oxidized by these two halogens.

VIII. ACTION OF ACID ON THIOSULFATES.

$$M''S_2O_3 + 2H^+ \rightarrow M^{++} + H_2O + SO_2 + S$$

A. The formation of sulfur according to this method by the action of excess hydrochloric acid on calcium thiosulfate has already been encountered in the preparation of Precipitated Sulfur (p. 94).

B. $Na_2S_2O_3 + 2HCl \rightarrow$

$2NaCl + H_2O + SO_2 + S$

This reaction is used in the U.S.P. identification test for thiosulfates[29] and also is used as a test for thiosulfate impurity in the U.S.P. Potassium Iodide and Sodium Iodide.[30] It also explains why titrations with sodium thiosulfate solutions cannot be carried out in acid media.

A strong acid, such as sulfuric or hydrochloric, is not necessary to bring about this

decomposition. Even as weak an acid as carbonic, or carbon dioxide, is sufficient to cause the deterioration of a standard solution of sodium thiosulfate, and for this reason it is necessary to protect such solutions from the CO_2 of the air and to restandardize them frequently.[31,*] It should be noted in this connection that a solution of sodium thiosulfate after having been exposed to the action of CO_2 becomes stronger, instead of weaker, in its action toward iodine because the reducing action of the sulfur dioxide formed is twice that of the sodium thiosulfate from which it is formed. One molecule of iodine is equivalent to two molecules of sodium thiosulfate and only one molecule of sulfur dioxide:

$$2Na_2S_2O_3 + I_2 \rightarrow 2NaI + Na_2S_4O_6$$

$$SO_2 + H_2O + I_2 \rightarrow 2HI + SO_3$$

IX. Reaction of Hydrogen Sulfide with Sulfur Dioxide.

$$2H_2S + SO_2 \rightarrow 2H_2O + 3S$$

* It has been shown that certain bacteria also cause a similar deterioration of sodium thiosulfate solutions. The use of a small amount of sodium carbonate prevents this type of deterioration by neutralizing any free thiosulfuric acid that may be formed before it decomposes farther. For the same reason of stability the hydrogen-ion concentration of the N.F. Ampuls of Sodium Thiosulfate is adjusted to a pH of 8.0 to 9.5.

This mutual oxidation-reduction reaction has already been referred to as one explanation of the formation and deposition of sulfur in volcanic regions (p. 92) and as a possible reaction which occurs when an excess of hydrochloric acid is added in the preparation of Precipitated Sulfur (p. 94). It is also utilized as a method for the preparation of the so-called colloidal sulfur, a finely divided, "wetable" form of sulfur which has received publicity as a therapeutic agent. It may be prepared by passing a stream of hydrogen sulfide through a cold aqueous solution of sulfur dioxide. The above reaction is accompanied by others, and the resulting reaction mixture contains polythionic acids (p. 146) in addition to sulfur.

Physical Properties. The chief physical properties of the elements of the oxygen or sulfur subgroup are summarized in Table 16.

There are at least four commonly known allotropic forms of sulfur.[32] *Rhombic sulfur*, the most stable form below 96° C., is a yellow solid; sp. gr. 2.07, m.p. 112.8° C. It is best obtained by allowing a carbon disulfide solution of commercial sulfur to evaporate slowly. Roll Sulfur and Flowers of Sulfur, the Sublimed Sulfur of the U.S.P., are mixtures of this form with the amorphous form. *Monoclinic sulfur* is obtained most easily by melting sulfur and allowing it to cool slowly.

Table 16. Properties of the Elements of the Oxygen or Sulfur Subgroup

Name	Oxygen	Sulfur	Selenium	Tellurium
Atomic weight	16.00	32.06	78.96	127.61
Physical state	Gas	Solid	Solid	Solid
Color	Colorless	Yellow	Red or gray	Gray, metallic
Specific gravity	0.001429 (0° C.)	1.96-2.07	4.5-4.8	6.24
Melting point (°C.)	−227	114.5	217	450
Boiling point (°C.)	−182.5	450	690	1,400
Solubility in water	1 cc. in 32 cc. (20° C.)	Insoluble	....	....
Solubility in alcohol	1 cc. in 7 cc. (20° C.)	Sparingly soluble	....	....

If the crust which forms on top of the cooled mass is broken, the long, transparent, needle-like crystals of monoclinic sulfur may be seen. This form has a sp. gr. of 1.96 and a m.p. of 119° C. It is stable only above 96° C., and on cooling, the crystals slowly change to the rhombic form.

Sulfur, when heated, melts at about 115° C., forming a yellow, mobile liquid which at a higher temperature, around 160° C., becomes darker in color and more viscous until it will not pour. At a still higher temperature, the sulfur becomes liquid again and boils around 450° C. If the viscous liquid is cooled suddenly, it yields a semisolid, transparent, elastic mass which can be drawn out into thin threads and is known as *plastic sulfur.* This is an unstable form which becomes opaque and brittle upon standing, leaving a residue of rhombic and *amorphous sulfur,* the latter being noncrystalline and having no definite melting point. At room temperature it changes slowly into the rhombic form. From the vapor state, sulfur solidifies into a mixture of the rhombic and amorphous forms.

The solubilities of the different forms of sulfur differ in most organic solvents. The U.S.P. forms of sulfur do not necessarily represent the different allotropic forms. In chemical reactions, with slaked lime, for example, the allotropic forms all undergo the same reactions.

Selenium and tellurium, like sulfur, exist in allotropic modifications.

Chemical Properties. To the union of oxygen with other elements, whether metallic to form bases or nonmetallic to form acids, Lavoisier (p. 38) originally applied the term oxidation. This is the most characteristic chemical property of oxygen—its ability to combine directly with all other elements except the halogens, the inert gases and the noble metals. This combination takes place slowly at ordinary temperatures, but when heated, the reactions take place rapidly and with the evolution of much heat.

Oxygen is not only the supporter of ordinary combustion, a property used in its identification,[33] but also is the supporter of respiration, hence its universality in all of the chemical processes within us and around us and also its use in the stimulation of respiration in disease.

Sulfur likewise combines directly with most metals and nonmetals, also with oxygen and the halogens, when the elements are heated together. It is readily oxidized by oxygen, by concentrated sulfuric acid and by other oxidizing agents, and reacts readily with metallic hydroxides and carbonates, especially those of the alkali and alkaline earth metals (p. 124).

Chemically, the members of this group resemble each other as the halogens resemble each other. They form similar compounds and one can be substituted for the other. For example, many hydrocarbons ignited in the air are incompletely burned to carbon dioxide and water and leave a deposit of carbon; when heated with sulfur, they yield carbon disulfide and hydrogen sulfide, and leave a deposit of carbon. This is sometimes used in the identification of substances like Paraffin.[34]

Toward hydrogen and other electropositive elements or groups, the elements of this group exhibit a negative character with a valence of minus two, forming oxides, sulfides, etc., as H_2O, H_2S, H_2Se, H_2Te, FeO, FeS, BaO, BaS, PbO, PbS, etc. The stability of the dihydrides of these elements decreases with an increase of the atomic weight of the element; thus water, H_2O, is the most stable while hydrogen sulfide, H_2S, is much less stable.

The elements of this group combine with electropositive elements not only in the simple ratios of their respective valences, as H_2O, H_2S, PbO, PbS, etc., but also as higher oxides and sulfides as well (peroxides and persulfides), for example, H_2O_2, BaO_2, Na_2O_2, FeS_2, CaS_2, etc., from which the excess oxygen or sulfur is usually liberated by the action of acids (pp. 119, 127).

Toward oxygen and other electronegative elements or groups, the three other elements of this group exhibit a positive character with the most common valences of plus four and six, forming such oxygen compounds as SO_2, H_2SO_3, SO_3, H_2SO_4, etc. These will be referred to in more detail later (p. 129).

Uses. Oxygen is included in monograph in the U.S.P.; it is most commonly placed on the market compressed into metal cylinders. Medicinally, oxygen finds its greatest use as a supporter of respiration, for which purpose it is used under many circumstances, especially in debilitating diseases such as pneumonia and others; it is used in poisonings by carbon monoxide and other gases, in drownings and in conjunction with nitrous oxide and other gaseous anesthetics for general anesthesia. It is supplied to airplane pilots at high altitudes and to divers in submarine rescue and salvage work. The chief industrial or technical use of oxygen is as a component of the oxyhydrogen and oxyacetylene torches, which are used for welding and cutting of metals because of the intense heats which they produce.

Sulfur is included in monograph in its three common medicinal forms: Precipitated Sulfur and Sublimed Sulfur (Flowers of Sulfur) in the U.S.P. and Washed Sulfur in the N.F. In addition, it is contained in the U.S.P. Sulfur Ointment and in the N.F. Alkaline Sulfur Ointment and Compound Sulfur Ointment (Wilkinson's Ointment or Hebra's Itch Ointment). Sulfur has enjoyed great popularity in medicinal use from the time of the ancients. It has been administered internally for its mild laxative action and as an alterative in conditions of constipation, dysentery and for various skin and liver diseases. As a "blood purifier" and general tonic, sulfur-and-molasses was at one time a common household remedy. Externally, in the form of an ointment or lotion, sulfur is used widely in the treatment of scabies and other skin diseases, such as psoriasis, acne, eczema, etc. Large quantities of sulfur are also used as a fumigating agent by burning and as an insecticide and fungicide or a component of insecticide and fungicide powders. In industry sulfur is used extensively in the manufacture of sulfuric acid, sulfur dioxide, sulfurous acid, sulfites and thiosulfates; in the vulcanizing of rubber and in the manufacture of gunpowder, matches and pyrotechnics, sulfur also is used.

Selenium and tellurium at present have no pharmaceutical applications or uses.

HYDRIDES OF THE ELEMENTS OF THE OXYGEN OR SULFUR SUBGROUP

The elements of the oxygen or sulfur subgroup, being divalent toward electropositive elements or groups, combine ordinarily with hydrogen to form the simple dihydrides, H_2O, H_2S, H_2Se, and H_2Te, in which each of the two valences of the divalent element is satisfied by monovalent hydrogen. Higher oxides and sulfides of hydrogen, such as H_2O_2, H_2O_4, H_2S_2, H_2S_4, H_2S_5, etc., are also known. The simple dihydrides of these elements will be considered now; the higher oxides and sulfides will be discussed in the next section.

Dihydrides

Occurrence. The occurrence of water is of such universality that little attention is paid to this subject. It is the medium in which all chemical reactions, both normal and pathologic, of plants and animals take place. The inanimate phenomena of nature are influenced by water as a mechanical, physical and chemical agent.

The occurrence of hydrogen sulfide in volcanic gases has already been referred to in connection with sulfur itself (p. 92). Hydrogen sulfide is also found in the animal organism as one of the products of intestinal putrefaction in the lower colon. Its occurrence in the plant kingdom, if not already

found there, may be postulated by inspection of the chemical structures of the sulfur-containing compounds isolated from plant sources.

Methods of Formation and Preparation.

I. Direct Union of the Elements.

A. $2H_2 + O_2 \rightarrow 2H_2O \text{ gas} + 2 \times 58.3 \text{ Cal.}$

Although this is a strongly exothermic reaction, it requires energy to bring it about. This may be accomplished in one of several common ways.

1. By burning hydrogen in an atmosphere of oxygen: This is the reaction upon which the use of the oxyhydrogen torch or blast lamp is based. The temperature of this flame may reach 2,500° C. and suffices to fuse such metals as iron. Even platinum, which melts at 1,755° C., is easily melted in this flame.

2. By bringing oxygen and hydrogen into "solid solution" with finely divided platinum sponge, the temperature at which the elements will combine is greatly reduced. The platinum acts as a catalyst. This expedient was used in the Döbereiner tinder box, which occasionally has found a place as a chemical novelty on the cigar counter of drug stores as a lighter.

3. By passing the electric spark through a mixture of oxygen and hydrogen: This is used commonly as a lecture experiment in general chemistry to demonstrate that the composition of water results from the union of two volumes of hydrogen with one of oxygen.

B. $H_2 + S \rightarrow H_2S \text{ gas} + 2.7 \text{ Cal.}$

This reaction, as well as the analogous reactions with selenium and tellurium, takes place less readily than the union of hydrogen with oxygen and is much less strongly exothermic.

II. Reduction of Oxides and Sulfides with Hydrogen.

A. $Fe_2O_3 + 3H_2 \rightarrow 2Fe + 3H_2O$

Reduced Iron of the N.F.[35] (Iron by Hydrogen, Quevenne's Iron) is prepared by this method, water being formed in the process (p. 266).

B. $Ag_2S + H_2 \rightarrow 2Ag + H_2S$

This reaction will take place at a red heat.

III. Action of Acid on Oxides and Sulfides.

A. $M''O + 2H^+ \rightarrow M^{++} + H_2O$

This method of formation of water is so commonplace that it need scarcely be mentioned. Innumerable reactions encountered in the U.S.P. and N.F. assays and tests for identity are illustrations of it; a few of these are the assays of the U.S.P. Magnesium Oxide,[36] Zinc Oxide,[37] Lead Monoxide[38] and others. The significance of the role played by water in these reactions sometimes is overlooked. It is partly because of the strongly exothermic character of the reactions by which water is formed and its thermal properties (p. 26) that acids and bases have a great affinity for each other and react to form salts.

B. $M''S + 2H^+ \rightarrow M^{++} + H_2S$

This reaction is commonly used as a test for the identification of metallic sulfides.[39]

1. $FeS + H_2SO_4 \text{ (or } 2HCl) \rightarrow FeSO_4 \text{ (or } FeCl_2) + H_2S$

This is the common method for preparing Hydrogen Sulfide U.S.P. in the laboratory or on a commercial scale.[40] Since the iron sulfide may contain some metallic iron, the resulting gas may also contain hydrogen.

2. $CaS_5 + 2HCl \rightarrow CaCl_2 + 4S + H_2S$

This reaction, already referred to under the preparation of Precipitated Sulfur (p. 94), is also used as a test for the identity of the N.F. Sulfurated Lime Solution (Vleminckx' Solution).[41]

3. $K_2S_n + 2CH_3COOH \rightarrow 2CH_3COOK + nS + H_2S$

This reaction is used as a test for the identity of the N.F. Sulfurated Potash (Liver of Sulfur).[42]

IV. Action of Acid on Hydroxides and Thiohydroxides.

A. $M'OH + H^+ \rightarrow M^+ + H_2O$

Directly comparable to the reaction between an oxide and an acid, this reaction between hydroxide and acid is of like significance and of corresponding frequency in the U.S.P. and N.F. assays and tests, a few of which are the assays of the U.S.P. Potassium Hydroxide,[43] Hydrochloric Acid,[44] Milk of Magnesia [45] and others.

B. $M'SH + H^+ \rightarrow M^+ + H_2S$

Pharmaceutical examples of this reaction are not commonly known.

V. Action of Acid on Alcohols (Organic Hydroxides).

A. $R—COOH + HOR' \rightarrow R—CO—O—R' + H_2O$

This reaction, commonly known as esterification, is as common in organic chemistry as the reaction between a hydroxide and an acid is in inorganic chemistry. Both the organic ester and water are formed, and the reaction also depends, in part at least, on the thermal properties of the water formed. In this case, however, the chemical role played by the water cannot be ignored, for the reverse effect of the water on the ester (hydrolysis) is reflected in the yield of the ester. This reaction is used frequently in organic chemistry to illustrate the equilibrium of reversible reactions.

VI. Dehydration and Desulfhydration of Hydroxides and Thiohydroxides.

A. Many hydroxy compounds, both inorganic and organic, give up water from their structure upon being subjected to the action of heat or other dehydrating agents. A few examples can be cited:

1. $PO(OH)_3 \xrightarrow{\Delta} PO_2OH + H_2O$

Orthophosphoric acid, when heated, gives up water as shown and goes to the meta form.

2. $B(OH)_3 \xrightarrow{\Delta} BO(OH) + H_2O$

Boric acid when heated to 100° C. loses water to form metaboric acid.

B. $2As(SH)_3 \rightarrow As_2S_3 + 3H_2S$

When hydrogen sulfide is passed into a solution of a trivalent arsenic compound, such as arsenic trichloride, the thioarsenous acid which results from the primary reaction, in the presence of sufficiently strong acid, will split off hydrogen sulfide with the precipitation of arsenic trisulfide. Under favorable conditions this arsenic trisulfide can take on hydrogen sulfide again or ammonia, forming the corresponding thioarsenous acid or its ammonium salts. However, as soon as an acid is added to this solution, free thioarsenous acid again is liberated and breaks down into arsenic trisulfide and hydrogen sulfide. This reaction, which is encountered in the U.S.P. test for arsenic in Sublimed Sulfur,[46] will be considered in more detail (p. 199).

Physical Properties. Water is a clear, odorless, tasteless liquid, colorless when viewed in moderate quantity but possessing a bluish-green color when viewed in bulk. It is an almost incompressible liquid, a poor conductor of heat and a worse conductor of the electric current. Below 0° C. it occurs in the solid state as ice crystals and above 100° C. it occurs in the vapor state as steam. In passing from the solid state to the liquid state at 0° C., a certain amount of heat energy is required (latent heat of fusion of ice); this is 79.5 Cal./Kg. of ice. This energy transformation is reversible, the same amount of energy being evolved when water passes from the liquid to the solid state. In passing from the liquid to the vapor state at 100° C., another amount of heat energy is required (latent heat of steam or the heat of vaporization of water); this is 539.7 Cal./Kg. of water. This energy change like-

wise is reversible, the same amount of energy being evolved when steam at 100° C. is transformed into water at 100° C.

Hydrogen sulfide is a colorless, inflammable gas, of sweetish taste and possessing a powerful and unpleasant odor resembling that of rotten eggs. It is heavier than air and is not readily soluble in water.

Chemical Properties. As shown by its heat of formation, +58.3 Cal., water is a very stable compound, easily formed and decomposed only with difficulty. Hydrogen sulfide, with a heat of formation of +2.7 Cal., is much less stable, being readily decomposed by oxygen and other oxidizing agents with the formation of water and the precipitation of sulfur. The significance of this property of hydrogen sulfide has already been noted under its formation and preparation (p. 102).

The high dielectric constant of water, together with its great solvent power, makes it an excellent ionizing medium for acids, bases and salts.

Water combines with the oxides of the metals to form bases and with the oxides of the nonmetals to form acids:

$$CaO + H_2O \rightarrow Ca(OH)_2$$

$$SO_3 + H_2O \rightarrow H_2SO_4$$

It unites with many salts to form hydrates:

$$MgSO_4 + 7H_2O \rightarrow MgSO_4 \cdot 7H_2O$$

Water also plays an important role in many hydrolytic reactions. Some salts, arsenic triiodide, for example, are almost completely hydrolyzed in acid solution, with the formation of arsenous acid and hydriodic acid (p. 40). Salts of strong bases and weak acids, such as sodium acetate, sodium bicarbonate and others, undergo hydrolysis in water to give solutions which are basic in reaction because of the formation of a weakly ionized acid and a strongly ionized base. Other salts of weak bases and strong acids, such as ammonium chloride, alum, etc., undergo hydrolysis in water to give solutions which are acidic in reaction because of the formation of a weakly ionized base and a strongly ionized acid. These hydrolytic reactions are of significance not only in the chemistry laboratory but also in the dispensing laboratory and are frequent sources of prescription incompatibilities.

Many of the chemical properties of hydrogen sulfide have already been referred to, especially its dissociation and ease of oxidation. Its decomposition by the halogens also has been noted (p. 40). When burned in the presence of excess oxygen it yields water and sulfur dioxide:

$$2H_2S + 3O_2 \xrightarrow{\Delta} 2H_2O + 2SO_2$$

The action of hydrogen sulfide as a reducing agent toward sulfur dioxide has been noted (p. 99). Even with sulfuric acid and nitric acid it acts as a reducing agent:

$$3H_2S + 2HNO_3 \rightarrow 4H_2O + 2NO + 3S$$

An aqueous solution of hydrogen sulfide is weakly acid toward litmus and is known as hydrosulfuric acid. It behaves in many ways as a weak acid, reacting with metals to form metallic sulfides and hydrogen:

$$H_2S + 2Ag \rightarrow Ag_2S + H_2$$

It also reacts with many basic oxides and hydroxides:

$$H_2S + KOH \rightarrow KSH + H_2O$$

$$H_2S + PbO \rightarrow PbS + H_2O$$

$$H_2S + 2NH_4OH \rightarrow (NH_4)_2S + 2H_2O$$

Uses. The constant everyday use of water for a variety of purposes is so common that it scarcely need be mentioned. Water has been quite appropriately designated as a universal solvent and, as already mentioned, it is the medium in which all the chemical processes of living organisms take place. Aside from this, its medicinal importance as a cleansing agent, as a vehicle for medicinal agents and foods and as a therapeutic agent, per se, in hydrotherapy gives it universal significance.

TABLE 17. U.S.P. FORMS OF WATER

FORM	pH	TOTAL SOLIDS	BACTERIAL CONTENT
Water	5.5 to 8.3	Not more than 0.1 per cent	Meets U. S. Public Health Service standards
Distilled Water	5.0 to 7.0	Not more than 0.001 per cent	Meets U. S. Public Health Service requirements
Sterile Distilled Water	5.0 to 7.0	Not more than 0.001 per cent	Meets requirements of U.S.P. Sterility Tests for Liquids
Water for Injection	5.0 to 7.0	Not more than 0.001 per cent	Meets requirements of U.S.P. Pyrogen Test

The four forms of water which are described in monograph in the U.S.P. are summarized, together with their requirements, in Table 17. Aside from the officially recognized forms of water, there are many other naturally occurring forms of water which are of significance in medicine and pharmacy. The solid ingredients of natural waters vary greatly in nature and quantity according to their source, locality, time of year, etc. Potable water, used for drinking purposes, may contain many of these dissolved solids without being injurious to the health. Such water, however, must be kept free from disease-producing microorganisms and a bacteriologic examination of water is one of the routine tasks of state and municipal health laboratories.

WATER U.S.P., potable water or drinking water, is not suitable for general pharmaceutical use because of the amount of dissolved solids which it contains. A range in hydrogen-ion concentration is allowed, between a pH of approximately 5.5 and 8.3, as denoted by its failure to give a red color with either methyl red or phenolphthalein indicators. The slight acidity or alkalinity of water may be due to dissolved solids as well as to dissolved carbon dioxide or ammonia. It is required to contain not more than 100 mg. of total solids in 100 cc. (0.1 per cent) and must meet the standards for freedom from coliform organisms that are set by the United States Public Health Service for potable water. A limit of heavy metals and zinc impurities is also set by the U.S.P.

DISTILLED WATER U.S.P. is water that is purified by distillation; it is used in general chemical and pharmaceutical practice and in the preparation of aqueous solutions except those which are to be administered by injection. The range in hydrogen-ion concentration is allowed to be between a pH of approximately 5.0 and 7.0, as denoted by its failure to give a red color with methyl red indicator or a blue color with bromthymol blue. It is required to contain not more than 1 mg. of total solids in 100 cc. (0.001 per cent). In other respects the requirements are much the same as for Water, except that the U.S.P. sets a limit for chloride, sulfate, ammonia, calcium and carbon dioxide content and also a limit on the content of oxidizable impurities.

In recent years there has been developed a method for the production of water of a quality and purity comparable to that of distilled water and at a lower cost. This process, which is based on the same principle of ion-exchange that is used in water softeners of the permutite and zeolite type, gives rise to the so-called deionized water, in which both cations and anions have been removed. The cations are removed by passing the water through a hydrogen-exchange resin, which converts the dissolved salts to the corresponding acids. The anions are then removed by passing the water through an-

other, basic, resin which unites with them. The U.S.P. and N.F. do not recognize this deionized water as a substitute for Distilled Water.

Sterile Distilled Water U.S.P. is Distilled Water that has been placed in sterile, suitable containers, properly sealed and sterilized. It is used for the preparation of medication in solutions which must be sterile, e.g., for use in the eye, urethra, etc., but not for parenteral injection. Sterilization may be accomplished in one of several different ways, but the U.S.P. recommends Process C, which is the use of steam under pressure. In addition to meeting the requirements for Distilled Water, Sterile Distilled Water must also meet the U.S.P. requirements under its Sterility Test for Liquids.

Water for Injection U.S.P. is the only form of water that is to be used for the preparation of medication for parenteral administration. It is distilled water which is sterile and also free from pyrogens (fever-producers). It may be used immediately after distillation, it may be kept overnight at a temperature which prevents bacterial growth or it may be packaged and sterilized for future use, in which case it must meet the U.S.P. requirements of the tests for sterility and clarity. In addition to the requirements under Distilled Water, the U.S.P. provides for Water for Injection a Pyrogen Test, to which it must conform.

Mineral waters are natural spring waters containing special mineral ingredients or dissolved gases which make them of some value as medicinal agents. These are usually distinguished by name: chalybeate waters contain iron salts which give them a characteristic taste; saline waters or bitter waters contain magnesium salts, especially the sulfate, along with sodium sulfate and others and are used for their purgative action; sulfur waters contain hydrogen sulfide and are characterized by their odor and taste; carbonated waters are charged with carbon dioxide in the earth, and they effervesce upon emerging; lithia waters contain lithium salts.

The household use of water as a cleansing agent and for cooking is affected by the hardness of the water. This property is due to variable amounts of calcium, magnesium, and, to a lesser extent, iron salts dissolved in the water. These salts, in contact with soap, precipitate as the corresponding salts of the fatty acids in the form of an insoluble curd, preventing the formation of lather and hindering the cleansing action of the soap. Temporary hardness of water, caused by the presence of bicarbonates of calcium and magnesium, may be dispelled by boiling the water, thereby driving off CO_2 from the bicarbonates and precipitating the normal, insoluble carbonates of calcium and magnesium. Permanent hardness, on the other hand, which is caused by the presence of sulfates, chlorides, etc., of calcium and magnesium, cannot be dispelled by boiling; it must be treated with soluble carbonates which will cause the precipitation of insoluble calcium and magnesium carbonates or by means of a water softener of the ion exchange type (p. 218). The degree of hardness of water is commonly expressed in terms of grains of calcium carbonate per gallon of water or in terms of mg. of calcium carbonate per liter of water; it is determined by measuring the amount of a standard soap solution required to produce a permanent lather when shaken with a measured amount of the water.

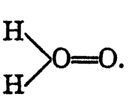
Hydrogen Sulfide is contained as a reagent in the U.S.P. and also as Hydrogen Sulfide Test Solution, a saturated aqueous solution of the gas. Both of these reagents are used innumerable times in the U.S.P. and N.F. in testing for heavy metals as impurities [47] and in the identification tests for various chemicals.[48] In fact, the most important use of hydrogen sulfide is as a reagent in qualitative chemical analysis. While it forms sulfides with most of the metals, the sulfides of the alkali and some of the alkaline earth metals such as sodium, potassium, magne-

sium, etc., are soluble in water; other sulfides such as those of iron, zinc, nickel, etc., are insoluble in water but soluble in dilute acids and still other sulfides, such as those of lead, copper, arsenic, etc., are insoluble in both water and dilute acids. By taking advantage of these differences in the solubility properties of the sulfides of the metals, a method for the detection and separation of mixtures of metals may be devised and followed successfully. This will be discussed in more detail (p. 125).

It should be emphasized that hydrogen sulfide is a very poisonous gas when inhaled in sufficient concentration and cases of acute toxicity should be treated by artificial respiration and oxygen therapy.[49]

Higher Oxides and Sulfides of Hydrogen

In addition to the simple dihydrides, H_2O, H_2S, etc., in which each of the two valences of the divalent element is satisfied by monovalent hydrogen, the elements of this subgroup combine in a different ratio with hydrogen to form higher oxides and sulfides, such as H_2O_2, H_2S_2, H_2S_3, H_2S_5, etc. These higher oxides and sulfides combine two or more oxygen atoms or two or more sulfur atoms in a peroxide or a persulfide linkage, as H—O—O—H or



Occurrence. Of these higher oxides and sulfides, only hydrogen peroxide, H_2O_2, occurs for any length of time in the free state and even it is unstable. They occur chiefly in combination with metals as metallic peroxides or dioxides, persulfides and polysulfides. Indeed, the discovery of hydrogen peroxide itself, by Thenard in 1818, was made when he observed the action of dilute hydrochloric acid on the dioxides of the alkaline earth metals:

$$BaO_2 + 2HCl \rightarrow BaCl_2 + H_2O_2$$

Methods of Formation and Preparation.

I. Action of Water or Acid on Compounds Containing the Peroxide or Persulfide Structure.

A. $BaO_2 + H_2SO_4 \rightarrow BaSO_4 + H_2O_2$

This is one of the commercial methods for preparing hydrogen peroxide and is likewise used in the laboratory for preparing the U.S.P. Hydrogen Peroxide Solution. Phosphoric acid may be used in place of sulfuric acid.

In the laboratory preparation of a solution of hydrogen peroxide, crude barium peroxide is treated with an acid to liberate hydrogen peroxide:

$$BaO_2 + 2HCl \rightarrow BaCl_2 + H_2O_2$$

The hydrogen peroxide thus formed is reconverted into pure barium peroxide by treating it with a solution of barium hydroxide to remove the impurities (ferric, manganic and aluminum oxides) from the original crude barium peroxide; the solution of hydrogen peroxide as obtained above is made just alkaline by addition of barium hydroxide solution. This forms the insoluble hydroxides of the metallic impurities, which are removed by filtration, and the filtrate then is treated with more barium hydroxide solution to form a precipitate of pure barium peroxide octahydrate:

$$H_2O_2 + Ba(OH)_2 + 6H_2O \rightarrow BaO_2 \cdot 8H_2O$$

The hydrogen peroxide is finally obtained from this pure barium peroxide octahydrate by treating it with an acid as above; phosphoric acid is preferred because the precipitated barium phosphate is removed more easily from the resulting solution of hydrogen peroxide:

$$3BaO_2 \cdot 8H_2O + 2H_3PO_4 \rightarrow Ba_3(PO_4)_2 + 8H_2O + 3H_2O_2$$

B. $Na_2O_2 + 2H_2O \rightarrow 2NaOH + H_2O_2$

or

$$Na_2O_2 + H_2SO_4 \rightarrow Na_2SO_4 + H_2O_2$$

When Sodium Peroxide U.S.P. Reagent is dissolved in water, hydrogen peroxide is formed and gradually breaks down with the evolution of oxygen. Hydrogen peroxide is prepared commercially by the action of sulfuric acid on sodium peroxide. This reaction is also encountered in the assay of Sodium Peroxide.[50]

C. $CaS_5 + 2HCl \rightarrow CaCl_2 + H_2S_5$

This reaction has been mentioned in the preparation of Precipitated Sulfur (p. 94). When the solution of polysulfides of calcium is treated with hydrochloric acid, the reaction by which sulfur is precipitated presumably takes place in two steps, the hydrogen pentasulfide further breaking down to sulfur and hydrogen sulfide. This assumption is verified by the fact that when the process is reversed and the solution of calcium polysulfides is poured into hydrochloric acid, a mixture of hydrogen persulfides separates as a yellow, oily layer and very little H_2S is formed. The mixture of hydrogen persulfides is unstable; when mixed with water it decomposes into hydrogen sulfide and sulfur.

D. $NaBO_2 \cdot 3H_2O \cdot H_2O_2 + H_2O \rightarrow NaBO_2 + 4H_2O + H_2O_2$

or

$$2NaBO_2 \cdot 3H_2O \cdot H_2O_2 + H_2SO_4 \rightarrow Na_2SO_4 + 2HBO_2 + 6H_2O + 2H_2O_2$$

Sodium Perborate U.S.P. (which is more properly written as above and not as $NaBO_3 \cdot 4H_2O$ as given in the Pharmacopœia),[51] when treated with water or with an acid in the presence of water, liberates its hydrogen peroxide. It is because of this reaction and the subsequent liberation of oxygen by the hydrogen peroxide that sodium perborate finds use as an antiseptic agent, especially in the oral cavities. It is also because of these reactions that a solution of sodium perborate, when used for such purpose, should always be freshly prepared since it loses its antiseptic power upon standing (p. 236).[52]

E. $H_2S_2O_8 + 2H_2O \rightarrow 2H_2SO_4 + H_2O_2$

The hydrolysis of persulfuric acid, or peroxydisulfuric acid, as shown in this equation, is also a commercial method for the preparation of hydrogen peroxide, concentrations up to 30 per cent being obtained by this method. The persulfuric acid is commonly prepared by electrolysis of cold aqueous solutions of metallic acid sulfates, such as ammonium acid sulfate (p. 146).

F. $$\begin{array}{l} C_6H_5\text{—}CO\text{—}O \\ \qquad\qquad\quad | \\ C_6H_5\text{—}CO\text{—}O \end{array} + 2H_2O \rightarrow 2C_6H_5COOH + H_2O_2$$

Organic peroxides, such as benzoyl peroxide, yield hydrogen peroxide upon hydrolysis. Since it is miscible with organic liquids, benzoyl peroxide finds use as a bleaching agent for fats, oils, waxes, etc.

Physical Properties. Pure hydrogen peroxide is a colorless, oily liquid with a specific gravity of 1.465. It is soluble in all proportions in water, alcohol and ether and it can be crystallized in colorless, prismatic crystals from a concentrated solution. In the solid form it melts at approximately −1° C. and boils at 69° C. under 29 mm. pressure.

Hydrogen persulfide, H_2S_2, is a heavy, yellow oil, specific gravity 1.334, with a characteristic pungent sulfurous odor. It is insoluble in and decomposed by water, but is readily soluble without decomposition in ether. It is inflammable and burns with a blue flame. H_2S_2 can be distilled at normal pressure, boiling at 70.7° C.; it solidifies at −89° C.

Chemical Properties. Hydrogen peroxide and hydrogen persulfide resemble each other in their chemical behavior, as would be expected from their similar formulae. Hydrogen peroxide is unstable, parting with half its oxygen and reverting to water. This decomposition takes place slowly even at ordinary temperatures and more rapidly when heated. The decomposition is accelerated by many other agents, including light, agitation, alkali, metals and

oxidizing as well as reducing agents. The presence of a trace of acid as well as certain negative catalysts serve to inhibit its decomposition. Because of this ease of decomposition, the U.S.P. directs that Hydrogen Peroxide Solution be stored at lower temperatures, protected from light and also allows the presence of a limited amount of preservative, usually acetanilid.[53] Solutions containing as high as 30 per cent H_2O_2 are available on the market; during World War II German chemists and engineers improved methods of concentration of hydrogen peroxide solutions and methods of storage to such an extent that concentrations as high as 90 per cent H_2O_2 are now commercially available and may be stored with comparatively little instability and safety hazard.

The ease of decomposition of hydrogen peroxide accounts for most of its uses as an oxidizing agent. One of the common tests for identity of hydrogen peroxide also depends upon its oxidizing action:

$$2KI + H_2O_2 \rightarrow 2KOH + I_2$$

Thus, when starch-potassium iodide paper is moistened with hydrogen peroxide solution a blue color appears, due to the formation of iodine which gives a blue color with the starch. The U.S.P. test for identity, using potassium dichromate in presence of dilute sulfuric acid, depends upon the appearance of a blue color which dissolves in ether. The blue-colored compound is said to be a perchromic acid.[54]

Although hydrogen peroxide is a good oxidizing agent, it also acts as a reducing agent under certain conditions, exerting its reducing action by parting with half its oxygen. This apparently contradictory behavior is noted in the U.S.P. description of Hydrogen Peroxide Solution as well as in its assay procedure (p. 97), where the hydrogen peroxide is oxidized by potassium permanganate, giving up half of its oxygen to form molecular oxygen with that contributed by the permangate.

The same reducing action of hydrogen peroxide is illustrated in its reaction with certain metallic oxides, the oxide being reduced to the free metal at the same time hydrogen peroxide is decomposed to water and oxygen:

$$Ag_2O + H_2O_2 \rightarrow 2Ag + H_2O + O_2$$

Such metals possess only a weak power of combination with oxygen, and their oxides decompose easily into the elements. When these oxides react with hydrogen peroxide, which in itself contains one atom of oxygen feebly combined, an analogous reduction takes place, the oxygen of the peroxide combining with the oxygen of the metallic oxide to form molecular oxygen.

Hydrogen peroxide in aqueous solution reacts as a feeble acid; as such it will react with weak bases to form metallic salts of hydrogen peroxide or metallic peroxides:

$$Ca(OH)_2 + H_2O_2 \rightarrow CaO_2 + 2H_2O$$

Utilization of this property in the laboratory preparation of hydrogen peroxide solution has already been mentioned (p. 107).

Hydrogen persulfide, H_2S_2, the counterpart of hydrogen peroxide, is also very unstable and is gradually decomposed into hydrogen sulfide and free sulfur:

$$H_2S_2 \rightarrow H_2S + S$$

This decomposition is also hastened by higher temperatures and light. Hydrogen persulfide also is decomposed by metallic oxides and behaves as a weak acid.

Uses. The uses of hydrogen peroxide are indicated by its properties. It is included in monograph in the U.S.P. in 3 per cent aqueous solution as Hydrogen Peroxide Solution and in the U.S.P. Reagents as Hydrogen Peroxide, 30 per cent. In addition, there is included in monograph Medicinal Zinc Peroxide, containing 45 per cent ZnO_2, which yields hydrogen peroxide by the action of water (p. 119).

Because of its ease of decomposition, hydrogen peroxide finds use as an oxidizing agent and as an antiseptic, germicide and

deodorant in medicine, especially in the form of a gargle and as a cleansing and antiseptic wash for open wounds. It is also used in its U.S.P. strength and in stronger concentrations as a bleaching agent, for bleaching hair, skin tissues, fabrics, and other substances where a mild, noncorrosive action is desired. Its use as a fuel for jet-propelled missiles was a recent war development.

The strength of hydrogen peroxide solutions frequently is expressed in terms of "volumes," this term being used to denote the volume of oxygen available from one volume of the peroxide solution at 0° C. and 760 mm. pressure.[55] Thus the 3 per cent solution is designated as "10 volumes peroxide," the 30 per cent solution as "100 volumes peroxide," etc. In addition to its aqueous solutions, hydrogen peroxide or its metallic salts, occurs on the market under various trade names in the form of cosmetic creams for bleaching purposes. It has already been mentioned (p. 108) that the use of Sodium Perborate U.S.P. as an antiseptic is due to the fact that this compound liberates hydrogen peroxide when treated with water.

Hydrogen persulfide and the other hydrogen polysulfides are not included in the U.S.P. or N.F. as such, but they are contained in the form of their potassium salts in Sulfurated Potash and in solution in the form of their calcium salts in Sulfurated Lime Solution (Vleminckx' Solution), both in the N.F.

OTHER ELEMENTS OF GROUP VI—THE CHROMIUM SUBGROUP

The elements included in this subgroup are chromium, molybdenum, tungsten and uranium. They exhibit only a few resemblances to the oxygen or sulfur subgroup in their properties, but among themselves they show definite resemblances in properties. On the whole, they are of less importance in pharmacy.

History. A naturally occurring chromium compound was reported about the middle of the eighteenth century in the mineral from Siberia called crocoite, which we now know as lead chromate, but the presence of a new element in this mineral was not finally recognized until Vauquelin, in 1797, found it to be a compound of lead in combination with an acid which he considered to be the oxide of a new metal. Klaproth, at the same time and independently of Vauquelin, came to the same conclusion. The name chromium, from the Greek word, *Chroma* (color), was given to it because all of its compounds were colored.

Scheele, in 1778, showed that the mineral molybdenite, heretofore considered identical with graphite or plumbago, upon treatment with nitric acid yielded an acidic compound which he called molybdic acid; a few years later Hjelm isolated the element by reduction of the molybdic acid with charcoal. In the discovery of tungsten again it was Scheele, in 1781, who demonstrated the presence of a new acid, which he called tungstic acid, in the mineral, scheelite; Bergmann in the same year recognized tungstic acid as the oxide of a new element, and a few years later the element itself was isolated by d'Elhujar.

Uranium was first detected in the mineral, pitchblende, by Klaproth in 1789 and named as such after the planet, Uranus, which had been discovered a few years previously. What was thought by Klaproth to be the element itself was later shown by Peligot to be an oxide of uranium and the latter isolated the element some years after Klaproth's discovery.

Occurrence. None of the metals of this subgroup appear free in nature. The chief naturally occurring combinations of chromium are chromite, $Fe(CrO_2)_2$ or $FeO \cdot Cr_2O_3$; chrome ochre, chiefly the sesquioxide, Cr_2O_3, in igneous rocks, and crocoite, $PbCrO_4$.

The principal ore of molybdenum is molybdenite, MoS_2, which is widely dis-

tributed; it also occurs as molybdates of certain heavy metals such as wulfenite, $PbMoO_4$, and as molybdite, the trioxide, MoO_3.

Tungsten occurs chiefly in the ore, wolframite, a mixture of ferrous and manganous tungstates, $FeWO_4 \cdot MnWO_4$; also in scheelite, $CaWO_4$, and in other metallic tungstates; and as wolfram ochre as the trioxide, WO_3.

Uranium occurs in pitchblende or uraninite as U_3O_8; it also occurs as carnotite, $KUO_2(VO_4) \cdot 3H_2O$, autunite, $Ca(UO_2)_2(PO_4)_2 \cdot 8H_2O$, and in several other minerals all of which are important as a source of radium.

Methods of Formation and Preparation. Since the methods of formation and preparation of these elements are not encountered in pharmacy, they will be only briefly summarized here. Chromium metal is used principally in the production of chrome steel, for which purpose ferrochrome is produced by reduction of chromite by carbon.

Pure chromium metal is produced by the "thermite" reduction of chromic oxide with aluminum or by the electrolysis of metallic chromate solutions; the latter process is used for chromium plating.

Molybdenum usually is obtained by roasting the native sulfide, molybdenite, to the trioxide, which is then converted into ammonium molybdate by washing with ammonia, and ignited again to the trioxide. The metal then is obtained by reduction of the oxide with carbon or by the "thermite" process as in the case of chromium.

Tungsten is obtained from wolframite ores by leaching with sodium carbonate to obtain sodium tungstate, which upon acidification and ignition yields the trioxide. The metal then is obtained by reduction of the oxide.

Uranium generally is obtained from pitchblende by converting it into the sulfate, UO_2SO_4, forming the oxide by ignition of the ammonium uranate, and reducing the oxide with carbon or other reducing agent.

Physical Properties. The physical properties of the elements of the chromium subgroup can best be summarized and compared in Table 18.

Chemical Properties. As mentioned previously, the elements of the chromium subgroup exhibit marked differences in properties from the elements of the oxygen or sulfur subgroup and the only marked similarities between the two subgroups is that the elements of both form trioxides which are acidic in character and give rise to salts of the type represented by metallic sulfates, chromates, uranates, etc. For this reason, the hexahydroxides of the elements of group VI are all treated together (p. 129).

The elements of the chromium subgroup are all characteristic metals which will combine directly with oxygen, sulfur and halogens. They do not form hydrides like the elements of the oxygen or sulfur subgroup. They are sometimes classed as transition elements, and show considerable resem-

TABLE 18. PROPERTIES OF THE ELEMENTS OF THE CHROMIUM SUBGROUP

NAME	CHROMIUM	MOLYBDENUM	TUNGSTEN	URANIUM
Symbol	Cr	Mo	W	U
Atomic weight	52.01	95.95	183.92	238.07
Color or appearance	Bluish-white, lustrous	Silver-white	Silver-white	White
Specific gravity	7.1	10.2	19.3	18.7
Melting point (°C.)	1,615	2,620	3,370	1,850

blance in properties to their horizontal neighbors in the periodic table, as exemplified in the resemblance between vanadium, chromium and manganese.

Toward electronegative elements or groups, the elements of this subgroup exhibit a positive character and variable valence. Thus, chromium most commonly exhibits valences of plus two, three and six; the other elements, in addition to those valences, also exhibit valences of plus four and five. All of the elements in their hexavalent state form oxychlorides of the same type as chromyl chloride, CrO_2Cl_2, which are hydrolyzed by water.

Chromium in its divalent state is represented as the basic chromous ion in the oxide, hydroxide, sulfate, halide, etc. In its trivalent state, the chromic ion acts both acidic and basic, forming such compounds as the oxide, hydroxide, sulfate and halide, while the hydroxide or the oxide may be dissolved by alkali hydroxides to form metallic chromites of the formula $M'CrO_2$. In its hexavalent state, chromium forms the trioxide, and the acidic chromate ion is represented in chromic acid and metallic chromates of the formula M'_2CrO_4.

Molybdenum, tungsten and uranium in their divalent states are represented by the halides; in the trivalent state, only molybdenum commonly forms compounds as the oxide, hydroxide, sulfide, etc. In their tetravalent states, all of these elements are represented in the dioxide, disulfide, tetrahalide, etc., while in their hexavalent states they, like chromium, form the trioxides and the corresponding molybdate, tungstate and uranate ions as represented in their "-ic" acids and the corresponding "-ate" salts. In the hexavalent state, with increasing atomic weight of the element, the basic character of the element reaches its height in uranium which, besides forming uranates of the formula M'_2UO_4, also forms salts like uranyl nitrate, $UO_2(NO_3)_2$, in which the uranyl radical acts like a base (p. 133). The most important properties of uranium are connected with its radioactivity.

Uses. None of the elements of this subgroup, as such, is used in pharmacy. Those compounds of the elements which have pharmaceutical uses or applications will be treated in their proper place.

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7

Metallic Oxides

THE METALLIC OXIDES

All metals combine directly or indirectly with oxygen to form the binary compounds known as oxides. Many of the metals combine to form more than one oxide while others form only one. For example, iron will form ferric oxide, Fe_2O_3, ferrous oxide, FeO, and ferrosoferric oxide, Fe_3O_4, but calcium normally forms only the simple oxide, CaO. These metallic oxides have the general formulas M'_2O, $M''O$, M'''_2O_3, etc. They are basic oxides and will form salts with acids. Many form hydroxides with water. In addition to the normal oxides, there are those compounds which may be considered to contain more oxygen than the highest oxide permitted by the position of the element in the periodic table. These high oxygen-containing oxides are known as peroxides and will be discussed further toward the end of this chapter. The hydroxides of the metals are known as bases; therefore, the corresponding oxides can be designated as basic anhydrides.

All of the nonmetals, with the exception of the inert gases, form oxides. These compounds are discussed under the various chapters pertaining to those elements. They are known as acidic oxides since they readily form hydroxides that have acid properties. The hydroxides of the nonmetals are designated as oxyacids, thus the corresponding oxides are acid anhydrides.

Occurrence. When consideration is given to the universality of oxygen and the comparative ease with which it combines with many metals to form oxides, it might be expected that these metals would be found in abundance as oxides in nature. Such is not the case, although they are widely distributed. Iron is found abundantly as red hematite, Fe_2O_3, and as magnetite or magnetic oxide of iron, ferrosoferric oxide, Fe_3O_4 or $FeO \cdot Fe_2O_3$. Aluminum oxide, Al_2O_3, is the basic compound in ruby, sapphire, emery and corundum. An important tin ore is known as tinstone and cassiterite; it is stannic oxide or SnO_2. The uranium ore, pitchblende, is U_3O_8. Some other oxide ores are chrome ironstone, Cr_2O_3, pyrolusite, MnO_2, and some copper ores.

Methods of Formation and Preparation.

I. Direct Combination of the Metal and Oxygen.

$$2M + O_2 \rightarrow 2M''O$$

A. $2Mg + O_2 \xrightarrow{\Delta} 2MgO$

Magnesium, in the form of ribbon or powder, will ignite readily, even from a lighted match; it burns with an intense white flame. Magnesium is an ingredient in many of the flash-powder formulas. It is the metal in the flash bulbs of photography and was used in certain types of incendiary bombs during World War II.

B. $4Fe + 3O_2 \xrightarrow{\Delta} 2Fe_2O_3$

Iron will combine with the oxygen of the air but reacts very readily in an atmosphere of pure oxygen at higher temperatures. Thus, steel wool will burn when heated to a red heat and placed in a container filled

with oxygen. Many other metals also form their oxides by direct combination.

II. Abstraction of Water from the Hydroxide.

$$M''(OH)_2 \xrightarrow{\Delta} M''O + H_2O$$

A. $Ca(OH)_2 \xrightarrow{\Delta} CaO + H_2O$

B. $2Fe(OH)_3 \xrightarrow{\Delta} Fe_2O_3 + 3H_2O$

C. $2AgOH$ * $\rightarrow Ag_2O + H_2O$

The ease of this reaction depends upon the electropositive character of the metallic ion. Yellow Mercuric Oxide N.F., for example, is prepared by the addition of an alkali hydroxide to a solution of a mercuric salt. It is believed that the hydroxide is formed first, but it is very unstable so that the oxide is produced without the application of heat.[1] Calcium hydroxide, like the hydroxides of many elements in groups I, II and III, will give up water only upon heating to a rather high temperature. The assay of Aluminum Hydroxide Gel [2] depends upon this type reaction.

III. Action of Oxygen upon Binary Compounds of Metals with the Elements of Higher Atomic Weight in the Same Subgroup.

$$2M''S \text{ (Se or Te)} + 3O_2 \xrightarrow{\Delta} 2M''O + 2SO_2$$

$$2HgS + 3O_2 \xrightarrow{\Delta} 2HgO + 2SO_2$$

This is the first reaction in obtaining mercury from cinnabar, a naturally occurring mercury sulfide. Arsenic Trioxide is another example that may be given here; it can be prepared from arsenic trisulfide.

IV. Heating of Oxysalts, for Example, Carbonates and Nitrates.

$$M''CO_3 \xrightarrow{\Delta} M''O + CO_2$$

$$2M''(NO_3)_2 \xrightarrow{\Delta} 2M''O + 2N_2O_4 + O_2$$

A. $CaCO_3 \xrightarrow[\text{Low Red Heat}]{\Delta} CaO + CO_2$

Calcium Oxide is commonly prepared by heating the carbonate; magnesium oxide is made by calcination of Magnesium Carbonate $(MgCO_3)_4 \cdot Mg(OH)_2$.†

B. $2Hg(NO_3)_2 \xrightarrow{\Delta} 2HgO + 2N_2O_4 + O_2$

Red Mercuric Oxide normally is obtained by carefully heating mercuric nitrate.

V. Breaking Down of a Higher Oxide (Including Peroxides) to a Lower Oxide and the Free Element.

$$2M''O_2 \xrightarrow{\Delta} 2M''O + O_2$$

$$3MnO_2 \xrightarrow{\Delta} Mn_3O_4 + O_2$$

This method may be used primarily for the preparation of oxygen on a laboratory scale (p. 93).

Properties and Uses. As a class, the oxides of metals are amorphous solids. Red Mercuric Oxide is, however, a red crystalline powder. Lead Monoxide is normally an orange powder, but it is fusible and may be obtained in a crystalline form. The oxides of the alkali metals, which have no direct use in pharmacy, are crystalline solids.

The oxides, with few exceptions, tend to react with water so that solubilities are dependent upon the rate of this reaction and the solubilities of the corresponding hydroxides.

Metallic oxides are normally classified as basic oxides, their basicity varying directly with the degree of electropositiveness of the metal; the more electropositive the metal, the more difficult it is to dehydrate the hydroxide. There are certain metallic oxides that form hydroxides which are amphoteric. Thus, aluminum hydroxide acts as a base when allowed to react with acids but it also

* The existence of silver hydroxide has been questioned.

† Magnesium Carbonate U.S.P. XIII is a "light" or bulky powder and will yield Magnesium Oxide U.S.P. XIII or Light Magnesia. A "dense" or heavy magnesium carbonate is required to produce the Heavy Magnesium Oxide U.S.P. XIII. (Note: Hot concentrated solutions of magnesium ions and carbonate ions will produce a dense precipitate when mixed.)

reacts as an oxyacid when brought in contact with alkali. The oxides of the strongly electropositive elements are very stable, e.g., the alkali metals,* whereas the oxides of more electronegative metals, e.g., mercury, silver and gold are dissociated easily by heat or light.†

Acids react with the metallic oxides to form the corresponding salts according to the type reaction:

$$M''O + 2H^+ \text{ (acid radical)} \rightarrow M'' \text{ salt} + H_2O$$

The so-called solubility of a metallic oxide in an acid is in reality the solubility of the salt in water or in a dilute acid solution.

OXIDES OF THE FORMULA M'_2O, OF PHARMACEUTICAL IMPORTANCE. None of the oxides of the alkali metals are of pharmaceutical importance as such. When the carbonates of these elements are heated above a dull red-heat, the oxides are formed to some extent. This is a condition which must be avoided in ash determinations.[3] The only possible important oxide of this type is mercurous oxide, which is said to be found in Black Lotion,[4] where it is prepared by the action of calcium hydroxide upon mercurous chloride according to the reaction

$$Ca(OH)_2 + 2HgCl \rightarrow Hg_2O + CaCl_2 + H_2O$$

It has been reported that x-ray studies have established only the presence of free mercury and mercuric oxide, so that the actual existence of such a compound may be doubtful.[5]

All of the oxides in this group, with the exception of mercuric oxide, slowly absorb water and carbon dioxide, forming carbonates and subcarbonates upon exposure to air. There are two forms of Magnesium Oxide described in the U.S.P. The titles are Magnesium Oxide and Heavy Magnesium Oxide. Magnesium Oxide, which is also known as Light Magnesia, is described "as a very bulky, white powder"; whereas Heavy Magnesium Oxide, which is also called Heavy Magnesia, is "a relatively dense, white powder." Both powders readily absorb water and carbon dioxide from the air. Both compounds are used as antacids or laxatives, depending upon the dose, so that the choice is a matter of pharmaceutical expediency. Where bulk is required, the

* These oxides will react readily with water and with carbon dioxide upon exposure to air. This is also true of the alkaline earth metallic oxides.

† See "packaging and storing" of Yellow Mercuric Oxide, U.S.P. XIII, p. 309. See also "residue on ignition," p. 308.

TABLE 19. OXIDES (M''O) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	COMMON NAME	SPECIAL FORMS	STORAGE
MgO	Magnesium Oxide	Magnesia Light Magnesia	Dusting powders; tooth powders and pastes	Airtight containers
MgO	(Heavy) Magnesium Oxide	Heavy Magnesia	....	Airtight containers
CaO	Calcium Oxide	Quick Lime Lime	....	Airtight containers
ZnO	Zinc Oxide	(See below for modifications)	Suspensions as lotions, etc., pastes, ointments and powders	Airtight containers
HgO	Mercuric Oxide (yellow)	Yellow precipitate	Ointment, lotion	Closed and light-resistant containers
HgO	Mercuric Oxide (red)	Red precipitate	Ointment	Closed and light-resistant containers
PbO	Lead Oxide	Litharge	....	Closed containers

Light Magnesia is the compound of choice.

Calcium Oxide is used in making the N.F. Solution of Sulfurated Lime and the commercial "Lime Sulfur" that is used as an insecticide. (See p. 94 for preparation of Precipitated Sulfur.)

Zinc Oxide is a somewhat unctuous white powder that is commonly employed in Zinc Oxide Ointment, which contains 20 per cent of the compound. It also is used in other preparations, especially in the Calamine Preparations, in certain pastes and in medicated dusting powders.[6] Calamine U.S.P.* is zinc oxide containing a small amount of ferric oxide, which gives the powder a pink color. Prepared Neocalamine N.F. contains 92 per cent of zinc oxide mixed with Red Ferric Oxide and Yellow Ferric Oxide which gives the powder a "flesh" color.

There are two official *Mercuric Oxides;* namely, Yellow Mercuric Oxide U.S.P. and Red Mercuric Oxide N.F. The yellow oxide is described as "a yellow to orange-yellow, heavy, impalpable powder," that gradually becomes black upon exposure to light. The amorphous character of this form makes it more desirable for preparations such as ophthalmic ointments, ointments, etc. The Red Oxide is described "as heavy, orange-red, crystalline scales, or as a crystalline powder, acquiring a yellow color when finely divided."

* The student is advised to look up Calamine Lotion, Phenolated Calamine Lotion, Calamine Liniment, Calamine Ointment and the corresponding Neocalamine preparations of the U.S.P. and N.F.

Litharge, Lead Oxide, is used in the preparation of Lead Subacetate Solution, Lead Oleate and other pharmaceutical formulas. It is also used in the arts.

Aluminum Trioxide is the residue left after the ignition of the aluminum hydroxide in the assay of Aluminum Hydroxide Gel.

Arsenic Trioxide is a white, amphoteric powder. It will react with acids to form salts as demonstrated in "Arsenic Chloride Solution" N.F., in which 10 grams of Arsenic Trioxide are dissolved in a total volume of 1,000 cc. by the use of 50 cc. of Diluted Hydrochloric Acid. The probable reactions are indicated as follows:

$$As_2O_3 + 6HCl \rightleftharpoons 2AsCl_3 + 3H_2O$$

$$AsCl_3 + HOH \rightleftharpoons As(OH)Cl_2 + HCl$$

$$As(OH)Cl + HOH \rightleftharpoons$$
$$As(OH)_2Cl \rightleftharpoons As\begin{smallmatrix}\diagup O\\ \diagdown Cl\end{smallmatrix} + HOH + HCl$$

$$As(OH)_2Cl + HOH \rightleftharpoons$$
$$As(OH)_3 \rightleftharpoons As\begin{smallmatrix}\diagup O\\ \diagdown OH\end{smallmatrix} + HOH + HCl$$

This is typical of $M'''X_3$ compounds (p. 69).

Arsenic trioxide will react with alkali hy-

TABLE 20. OXIDES (M'''_2O_3) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	COMMON NAMES	STORAGE CHARACTERISTICS
Al_2O_3.........	Aluminum Trioxide	....	Stable
As_2O_3.........	Arsenic Trioxide	Arsenious Anhydride	Stable
	Arsenious Oxide	Arsenious Acid	......
		White Arsenic	
Sb_2O_3.........	Antimony Trioxide	....	Stable
	Antimonous Oxide		
Fe_2O_3.........	Ferric Oxide (yellow)	....	Stable
Fe_2O_3.........	Ferric Oxide (red)	....	Stable

droxides or carbonates to form water-soluble salts as illustrated by Potassium Arsenite Solution (Fowler's Solution) U.S.P.[7] In this preparation 10 Gm. of the oxide are dissolved in 1,000 cc. of an aqueous solution of 7.6 Gm. of potassium bicarbonate. The meta-arsenite is formed according to the reaction:

$$As_2O_3 + 2KHCO_3 \rightarrow 2KAsO_2 + 2CO_2 + H_2O$$

Arsenic trioxide is very slowly soluble in water to the extent of about 1 per cent.

Antimony Trioxide was included in the N.F. V but is no longer official. It is also an amphoteric oxide, being used to form antimony chloride and Antimony Potassium Tartrate, as well as certain antimonates.

The two *Ferric Oxides* differ in the requirements of Fe_2O_3 content. The N.F. requires that a freshly ignited Yellow Ferric Oxide contain not less than 97.5 per cent of Fe_2O_3, while the Red Ferric Oxide must contain not less than 90 per cent of Fe_2O_3.

ing properties, as illustrated in the test for the manganous ion according to the reaction:

$$2Mn(NO_3)_2 + 5PbO_2 + 6HNO_3 \rightarrow 2HMnO_4 + 5Pb(NO_3)_2 + 2H_2O$$

In this reaction the manganous ion is oxidized and converted to the permanganate ion, which produces a purple color.

Titanium dioxide is an insoluble, dead-white powder that is used in certain face powders and creams; it is an ingredient in Iso-Par ointment. It is also used in white paints. The special value of TiO_2 as a white pigment is its "covering power," which is described as about five times that of zinc oxide. Cosmetic formulas normally require not more than 5 per cent of the compound.

Manganese dioxide is used for the laboratory scale preparation of chlorine, using hydrochloric acid.

Other Metallic Oxides of Pharmaceutical Importance. Lead also forms the

Table 21. Oxides ($M''''O_2$) of Pharmaceutical Importance

Formula	Chemical Name	Color	Storage Characteristics
PbO_2	Lead Dioxide "Lead Peroxide"	Dark Brown	Stable
TiO_2	Titanium Dioxide	White	Stable
MnO_2	Manganese Dioxide	Black	Stable

The elements lead and titanium belong in group IV of the periodic table and should, therefore, normally form the $M''''O_2$ compounds. PbO_2, however, frequently is designated as lead peroxide since it forms $PbCl_2$ and free chlorine with hydrochloric acid. It can only be formed by the oxidation of lead monoxide and readily gives up one-half of its oxygen when heated. The use of lead dioxide as a reagent is based upon its oxidiz-

oxide Pb_3O_4, which is known as red lead or minium. It is an insoluble orange-red powder, is sometimes referred to as lead orthoplumbate and has the formula Pb_2PbO_4. It is of very little use in pharmacy now but was included in the N.F. V for use in making a special form of a plaster.

Chromium Trioxide, CrO_3, is an acidic oxide, and commonly is referred to as chromic anhydride or chromic acid (p. 112).

THE METALLIC PEROXIDES (SUPEROXIDES)

A true peroxide is, as has been stated previously, an oxide that contains a higher percentage of oxygen than the highest valence of the other element would permit. It contains the characteristic group —O—O— as

$$\left[\begin{array}{c} :\ddot{O}:\ddot{O}: \\ \cdot x \cdot x \end{array}\right]^{=}$$

and the metallic peroxide yields hydrogen peroxide upon the addition of a dilute acid (or water with the alkali peroxides). For example, sodium peroxide[8] must be stored in tight containers to prevent the action of water upon the compound and the liberation of oxygen. Consequently the so-called lead peroxide, PbO_2, is not a true peroxide.

Methods of Formation and Preparation.

I. Direct Combination of Metal with Oxygen (Under Special Conditions).

$$2M + O_2 \xrightarrow{\Delta} M'_2O_2$$

$$2Na + O_2 \xrightarrow{\Delta} Na_2O_2$$

Sodium and potassium peroxides are formed by burning the metals in oxygen. It may be assumed that the reaction first results in the formation of the oxide, which then is changed to the peroxide.

II. The Action of a Metallic Hydroxide on Hydrogen Peroxide.

$$M''(OH)_2 + H_2O_2 \rightarrow M''O_2 + 2H_2O$$

$$Ca(OH)_2 + H_2O_2 \rightarrow Ca_2O_2 + 2H_2O$$

In this reaction, the hydrate of the particular peroxide is formed.

Properties and Uses. The metallic peroxides are solids. They decompose rather than dissolve as such in water. They are unstable when exposed to moist air since they absorb water and carbon dioxide, thus liberating oxygen.[9] The reaction of sodium peroxide with water may be considered typical even though it is much more active than the peroxides of nonalkali metals.

$$Na_2O_2 + 2H_2O \rightarrow 2NaOH + H_2O_2\ (\rightarrow H_2O + O)$$

or

$$2Na_2O_2 + 2H_2O \rightarrow 4NaOH + O_2$$

Sulfuric acid will react with barium peroxide in the cold to form hydrogen peroxide, as illustrated in the reaction

$$BaO_2 + H_2SO_4 \rightarrow BaSO_4 + H_2O_2$$

On the other hand, free chlorine is liberated when hydrochloric acid in excess is added to the peroxides:

$$BaO_2 + 2HCl \rightarrow BaCl_2 + H_2O_2$$

$$H_2O_2 \rightarrow H_2O + O$$

$$2HCl + O \rightarrow Cl_2 + H_2O$$

As evidenced in the reactions just indicated, the metallic peroxides are strong oxidizing agents, their uses being based upon this important chemical property. The fact that the oxygen is liberated more slowly is claimed to be an advantage in their medicinal uses. They are not used internally.

Table 22. Metallic Peroxides of Pharmaceutical Importance

Formula	Name	Color	Storage
Na_2O_2	Sodium Peroxide	White or yellowish	Tight containers
ZnO_2	Zinc Peroxide	White or yellowish	Tight containers
BaO_2	Barium Peroxide	White or yellowish	Tight containers

Sodium peroxide is a hygroscopic compound containing not less than 90 per cent of sodium peroxide; it readily gives off

oxygen when added to water. According to New and Nonofficial Remedies,[10] it has been used in a paraffin or similar base as a paste for acne. It is listed in the U.S.P. as a reagent. An important laboratory use of this compound is in the Parr Bomb determinations of halogens, etc., where it is used as an oxidizing agent.

The U.S.P. Zinc Peroxide is listed under the title Medicinal Zinc Peroxide[11] and is defined as "a mixture of zinc peroxide, zinc carbonate, and zinc hydroxide. It contains not less than 45 per cent of ZnO_2." Since a pure sample of ZnO_2 was not available and apparently could not be prepared, the formula has been questioned.[12]

Barium Peroxide has been used in the preparation of hydrogen peroxide by the action of sulfuric acid. It is a grayish-white powder that contains about 9.45 per cent available oxygen.

Sodium Perborate U.S.P. decomposes into sodium metaborate and hydrogen peroxide when dissolved in water (p. 108).

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8

Metallic Sulfides

THE METALLIC SULFIDES

Binary compounds of metals and sulfur are known as metallic sulfides and are analogous to the metallic oxides. They may be regarded as compounds in which the hydrogen of hydrogen sulfide has been replaced by a metallic ion. The oxides are considered as dehydration products of the hydroxides; thus, the sulfides may be regarded as the desulfhydration products of the thiohydroxides (SH). When this replacement is only one-half completed, the compound is known as a bisulfide, an acid sulfide, a sulfhydride or as a hydrosulfide. Polysulfides, or persulfides, which are compounds somewhat analogous to peroxides, are also known.

Occurrence. Many of the ores are metallic sulfides. Zinc blende is chiefly zinc sulfide, ZnS, but it also contains some cadmium sulfide. Zinc blende is found in the United States, especially in Oklahoma and Kansas, but is also found in other states and countries. The principal source of mercury is its sulfide, HgS; the naturally occurring compound is known as cinnabar. This important ore is found in the western coast of the United States and more abundantly in Spain.

Galena, the important lead ore, is lead sulfide, PbS. It is found in the United States in what is called the tristate area which includes northeastern Oklahoma, southeastern Kansas and southwestern Missouri.

Other elements also occur in nature as sulfides. Some of them are copper, especially as cuprous sulfide, silver as argentite, antimony as antimonite, arsenic which occurs as As_2S_2 (realgar) and As_2S_3 (orpiment) and iron pyrites (also known as "fool's gold" because of its appearance as yellow crystals). Hydrogen sulfide is found in many natural waters, producing what is commonly known as "sulfur water." This compound is also present in some petroleum wells. Natural gas containing hydrogen sulfide is known as "sour gas."

Methods of Formation and Preparation.

I. Direct Combination of Metal with Sulfur.

$$2M + S \rightarrow M'_2S \text{ or } (M''S \text{ etc.})$$

A. $Fe + S \rightarrow FeS$

This reaction proceeds very rapidly when the mixture is heated.

B. $Zn + S \rightarrow ZnS$

Zinc sulfide not only occurs in nature, but also is frequently found as an impurity in zinc. Unless all of the sulfur is separated in the metallurgic process, the two elements will vaporize together and then sublime as zinc sulfide.

Many other elements will combine directly with sulfur, for example, arsenic will form As_2S_3. Since both arsenic and sulfur will sublime and arsenic is widely distributed, it is frequently an impurity in sublimed sulfur. Arsenic may also be present as an impurity in other chemicals when they are obtained from ores.

II. Action of Hydrogen Sulfide on Metallic Hydroxide or Oxide.

A. $2M'(OH) + H_2S \rightarrow M'_2S + 2H_2O$

$2NaOH + H_2S \rightarrow Na_2S + 2H_2O$

The water-soluble hydroxides undergo this reaction.

B. $M''O + H_2S \rightarrow M''S + H_2O$

$CaO + H_2S \rightarrow CaS + H_2O$

However, when solutions of metallic sulfides are saturated with H_2S, solutions of the bisulfides are obtained:

C. $M'_2S + H_2S \rightarrow 2M'HS$

$Na_2S + H_2S \rightarrow 2NaHS$

III. Interaction of a Sulfide and Water Solution of Metallic Salt.

A. *Action of Hydrogen Sulfide.*

$$M'' \text{ Salt} + H_2S \rightarrow M''S + 2H^+ \text{ (acid radical)}$$

1. $HgCl_2 + H_2S \rightarrow HgS + 2HCl$

This reaction is the basis for the heavy metals test.[1] In all of these tests, where heavy metals are present, a darkening of the solution due to the formation of a highly colored precipitate of the sulfide is a positive test, e.g.,

2. $Cu^{++} + H_2S \rightarrow CuS + 2H^+$
3. $Pb^{++} + H_2S \rightarrow PbS + 2H^+$

The test for heavy metals in water, distilled water and volatile oils is particularly for lead or copper that may have contaminated them from pipes, stills or containers.

There are several tests in the U.S.P. and N.F. that are applications of this general reaction. One such illustration is the test for "alkali and earths" in cupric sulfate.[2] The sample is dissolved in water, then made acid with hydrochloric acid and hydrogen sulfide is passed into the solution until all of the copper is precipitated.

$$CuSO_4 + H_2S \xrightarrow{HCl} CuS + H_2SO_4$$

The insoluble cupric sulfide is filtered out. The amount of alkali then is determined by evaporation of the residue and weighing. The alkali and alkaline earth sulfides are soluble in the hydrochloric acid solution.

4. $HgI_2 + H_2S \rightarrow HgS + 2HI$

Soluble mercuric salts yield a black precipitate with hydrogen sulfide. Mercurous sulfide is not known. Therefore, the formation of a black precipitate by the action of hydrogen sulfide upon a mercurous salt indicates the presence of a mercuric salt as impurity. In carrying out the above test in Yellow Mercurous Iodide N.F., an alcoholic solution is used because any mercuric iodide that might be present is much more soluble in alcohol than in water.[3]

The practical insolubility of mercuric iodide is taken advantage of in testing this compound for water-soluble mercuric salts, mercuric chloride, for example, by shaking the mercuric iodide with water, filtering and treating the aqueous filtrate with hydrogen sulfide. If no soluble mercuric salts are present, only a slight coloration will appear, but if they are present, black mercuric sulfide will be formed. This is encountered under Red Mercuric Iodide N.F.[4] The same method is used in testing Mercuric Salicylate N.F. for more soluble mercury compounds.[5]

The precipitation of mercuric sulfide by the action of hydrogen sulfide upon soluble mercuric salts in acid solution is also used as a method for assaying some mercuric compounds, such as Mercury Bichloride N.F. and others, by precipitating, drying and weighing as mercuric sulfide.[6]

5. $Pb(CH_3COO)_2 + H_2S \rightarrow PbS + 2CH_3COOH$

Neutral or nearly neutral solutions of lead salts yield a black precipitate of lead sulfide when treated with hydrogen sulfide. This is used in the test for the presence of alkaline earth metals as impurities in lead salts in the U.S.P. and N.F. The precipitated lead sulfide is filtered off, and the filtrate is evaporated to dryness and ignited. The limit of

residue is the basis for the alkaline earth metals test.[7]

6. $CdCl_2 + H_2S \rightarrow CdS + 2HCl$

Cadmium compounds in neutral, alkaline or not too strongly acid solution yield, with hydrogen sulfide, a bright yellow precipitate of cadmium sulfide. Cadmium sulfide is insoluble in solutions of alkali sulfides, alkali hydroxides and ammonium carbonate solution, and this difference in solubility serves to distinguish it from arsenic trisulfide, which is soluble in these reagents. This same test may be used for antimony and tin as impurities in arsenic compounds.

7. $2AsI_3 + 3H_2S \rightarrow As_2S_3 + 6HI$

$2AsCl_3 + 3H_2S \rightarrow As_2S_3 + 6HCl$

Arsenous compounds, in dilute hydrochloric acid solution, yield a lemon yellow precipitate when treated with hydrogen sulfide.[8] This yellow precipitate of As_2S_3 is insoluble in water and hydrochloric acid but soluble in solutions of alkali sulfides or ammonium sulfide and in ammonium carbonate solution. Upon the addition of ammonia water or ammonium carbonate solution, therefore, a reaction takes place to form ammonium sulfide:

$$2NH_4OH + H_2S \rightarrow (NH_4)_2S + 2H_2O$$

This ammonium sulfide dissolves the precipitate of arsenic trisulfide with the formation of the ammonium salt of thioarsenous acid:

$$As_2S_3 + 3(NH_4)_2S \rightarrow 2(NH_4)_3AsS_3$$

Arsenic Trisulfide will also dissolve in ammonium hydroxide. This property is utilized in the preparation of Washed Sulfur N.F.

8. $2SbCl_3 + 3H_2S \rightarrow Sb_2S_3 + 6HCl$

Compounds of trivalent antimony in hydrochloric acid solution yield an orange-red precipitate of antimony trisulfide when treated with hydrogen sulfide.[9]

9. $Bi_2O_3 + 3H_2S \rightarrow Bi_2S_3 + 3H_2O$

Bismuth compounds in solution and bismuth oxide yield black bismuth trisulfide when treated with hydrogen sulfide. This reaction is involved in the tests for identity[10] of bismuth compounds in the U.S.P. and N.F. and was formerly made use of in the assay of certain bismuth compounds by drying and weighing the bismuth trisulfide.

B. *Action of an Alkaline Sulfide.* In certain instances, as in the formation of cadmium sulfide and zinc sulfide, the presence of an acid, formed in the reaction when hydrogen sulfide is used for precipitating the metallic sulfide, decomposes the sulfide formed. Consequently, alkaline sulfides are ordinarily used in those cases for the formation of the sulfides:

1. $Zn(CH_3COO)_2 + (NH_4)_2S \rightarrow ZnS + 2CH_3COONH_4$

This reaction is involved in the tests for identity of zinc salts in the U.S.P. and N.F.[11] The presence of sodium acetate in a solution containing zinc salts reacts in a similar manner because of its buffering effect.

$$CH_3COONa + H_2O \rightarrow Na^+ + OH^- + CH_3COOH$$

$$Na^+ + OH^- + H_2S \rightarrow Na_2S + H_2O$$

2. $CdCl_2 + (NH_4)_2S \rightarrow CdS + 2NH_4Cl$

Cadmium salts, like zinc salts, yield a precipitate with hydrogen sulfide when the acid formed in the reaction is not too strong. When, however, a strong mineral acid results from the reaction, the cadmium sulfide is decomposed. In these cases, it is best to use ammonium sulfide to bring about the reaction. The precipitated cadmium sulfide is bright yellow in color and is not soluble in an excess of the reagent, in contrast to arsenic trisulfide.[12]

This property of cadmium sulfide was utilized in the U.S.P. IX assay for Crude Calcium Sulphide; this method is no longer official. In this assay, process ammonium

chloride solution was added to a solution of the calcium sulfide, forming ammonium sulfide by double decomposition:

$$CaS + 2NH_4Cl \rightarrow (NH_4)_2S + CaCl_2$$

Cadmium chloride solution was then added, with the precipitation of cadmium sulfide, and the excess of ammonium sulfide was washed out with dilute acetic acid, cadmium sulfide being unaffected by this weak acid. Upon the addition of hydrochloric acid, however, the cadmium sulfide was decomposed, liberating hydrogen sulfide, which then reacted with an 0.1 N iodine solution, previously added, forming hydriodic acid and sulfur. The excess of iodine was determined in the usual way.[13]

3. Solutions of manganous compounds yield, with ammonium sulfide solution, a flesh or salmon-colored precipitate of manganous sulfide which is decomposed by even so weak an acid as acetic acid.[14]

$$MnCl_2 + (NH_4)_2S \rightarrow MnS + 2NH_4Cl$$

$$MnS + 2CH_3COOH \rightarrow Mn(CH_3COO)_2 + H_2S$$

Such reactions are well known to the student of qualitative analysis, where they are used for separation and identification of many cations. The sulfides of the copper and arsenic groups are insoluble in acid solution and those of the aluminum and nickel groups are soluble. These latter compounds are precipitated by alkalies in the presence of ammonia.

IV. Reduction of a Sulfate or Sulfite.

$$M''SO_4 + 2C \rightarrow M''S + 2CO_2 \text{ (or 4CO)}$$

A. $CaSO_4 + 2C \rightarrow CaS + 2CO_2$ (or 4CO)

This reaction has been used for the preparation of Crude Calcium Sulphide U.S.P. IX. According to the U.S.P. IX, Crude Calcium Sulphide was prepared by heating exsiccated calcium sulfate with carbon mixed with starch. The starch charred, producing more carbon, and helped mechanically by preventing the formation of a solid mass. The product obtained in this way contains fewer impurities than the product obtained by double decomposition between sodium sulfide and calcium carbonate; hence, it is better fitted for pharmaceutical purposes. It may, however, contain calcium sulfate and carbon.

B. The preparation of sodium carbonate by the LeBlanc process (p. 41) furnishes an example of the reduction of a sulfate in this way:

$$Na_2SO_4 + 4C \rightarrow Na_2S + 4CO$$

Double decomposition between the sodium sulfide and calcium carbonate then yields calcium sulfide and the sodium carbonate:

$$Na_2S + CaCO_3 \rightarrow CaS + Na_2CO_3$$

This process may be made to yield not only sodium carbonate, but also both sodium and calcium sulfides. Sodium sulfide is soluble without decomposition and may thus be purified by recrystallization, yielding colorless, transparent crystals. The calcium sulfide, which is nearly insoluble in water, contains small particles of carbon and forms a gray mass. It may also contain some calcium sulfate, formed either by double decomposition between any unreduced sodium sulfate and calcium carbonate or by oxidation, from contact with the air, of calcium sulfide. Thus, when calcium sulfide is dissolved in acetic acid, a residue of calcium sulfate and carbon may remain.

V. Action of Sulfur on Carbonates or Hydroxides.

A. *Action on Carbonates.*

$$M'_2CO_3 + S_x \xrightarrow{\Delta} M'_2S + CO_2 + (M'_2S_2O_3 + M'_2S_{x'})$$

$$K_2CO_3 + S_x \xrightarrow{\Delta} K_2S + CO_2 + (K_2S_2O_3 + K_2S_{x'})$$

When potassium carbonate is mixed with sulfur and heated, the sulfide K_2S is formed, but the product will also contain potassium

thiosulfate and polysulfides. The reaction may be considered to take place in at least two steps:

$$M'_2CO_3 \rightarrow M'_2O + CO_2$$

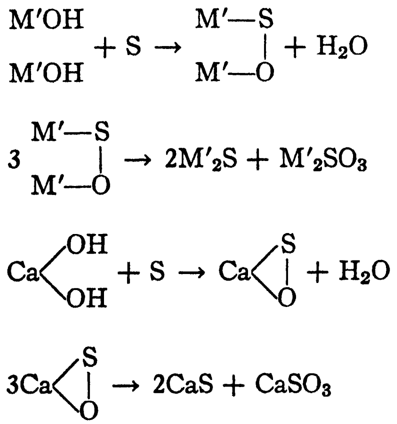
$$6M'_2O + S_x \rightarrow 2M'_2S + 2M'_2S_{x'} + 2M'_2S_2O_3$$

$$K_2CO_3 \rightarrow K_2O + CO_2$$

$$6K_2O + (S)_x \rightarrow 2K_2S + 2K_2S_{x'} + 2K_2S_2O_3$$

These reactions are involved when Sulfurated Potash N.F. is prepared by fusing potassium carbonate with sulfur. Sulfurated potash thus consists principally of the polysulfides of potassium and potassium thiosulfate.[15] The complex mixture varies in the relative proportions of each of the constituents, depending upon the quantities of materials used, the temperature of the reaction and the access of air to the reaction mixture.

B. *Action on Hydroxides.*



This reaction takes place when calcium hydroxide (Slaked Lime) is heated with sulfur in water. With an excess of sulfur, both the sulfide and the sulfite react with additional sulfur and form $CaS_2 \ldots CaS_5$ and CaS_2O_3; the final solution is a dark orange-colored liquid as exemplified in the N.F. Sulfurated Lime Solution.[16] These reactions have also been discussed in the preparation of Precipitated Sulfur (p. 94).

Properties and Uses. **The sulfides of the formula M'_2S, where M′ represents an alkali metal or ammonium, are soluble in water,** forming alkaline solutions that are caustic. These solutions are unstable, due to the action of oxygen of the air, and turn yellow according to the reactions:

$$2M'_2S + 4H_2O \rightleftharpoons 4M'OH + 2H_2S$$

$$2H_2S + O_2 \rightleftharpoons 2H_2O + 2S$$

$$M'_2S + S_x \rightleftharpoons M'_2S_{x+1}$$

Upon prolonged standing with access to air, a colorless solution is produced; the sulfide is oxidized to the thiosulfate, and sulfur is precipitated by carbon dioxide.

Where M′ represents a heavy metal, such as Cu, Ag, etc., the sulfides are insoluble in water.

The alkaline earth sulfides of the general formula M″S are practically insoluble in water but are hydrolyzed by this solvent producing the hydrosulfides. The other sulfides of this type formula are also insoluble in water but are not hydrolyzed by it.

Aluminum Sulfide, Al_2S_3, a M'''_2S_3 sulfide, can only be prepared in the absence of water since it hydrolyzes to form the hydroxide of the metal.

Metallic sulfides react with oxygen to form the corresponding oxide when subjected to increased temperature. Many sulfides react with acids and with acid salts to liberate hydrogen sulfide; however, the so-called "Hydrogen Sulfide Group" of qualitative analysis does not react in this manner. This group consists of PbS, HgS, Bi_2S_3, CuS, CdS, As_2S_3, Sb_2S_3 and SnS_2. The Ammonium Sulfide Group consists of the following ions: Al, Cr, Zn, Mn, Fe, Ni and Co. The sulfides of these metals are soluble in acid but will not dissolve in water when ammonium salts are present. These reactions should be remembered when working with any of the sulfides; they may produce desirable or undesirable precipitates.

These compounds are not used in pharmacy except as chemical reagents, primarily for the formation of sulfides by interaction with other soluble salts. $Na_2S \cdot 9H_2O$ is described in the U.S.P. under Reagents as

TABLE 23. SULFIDES (M'S) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)		CHARACTERISTICS IN STORAGE
		In Water	In Alcohol	
$Na_2S \cdot 9H_2O$...	Sodium sulfide	1-0.8	Soluble	Deliquescent and unstable
$K_2S \cdot 5H_2O$....	Potassium sulfide	Freely soluble	Soluble	Deliquescent and unstable
$(NH_4)_2S$......	Ammonium sulfide	Freely soluble	Soluble	Unstable

"clear, colorless, deliquescent crystals" having an odor of hydrogen sulfide. Ammonium Sulfide Test Solution U.S.P. is prepared by passing hydrogen sulfide into Ammonia T.S.[17] This solution must be stored in well-filled amber bottles and in a cool place to minimize the separation of sulfur. This test solution is used in the identity tests for iron compounds. Ferrous and ferric ions produce a black precipitate which is soluble in dilute hydrochloric acid. It is also used to test for manganese.

TABLE 24. SULFIDES (M"S) OF PHARMACEUTICAL IMPORTANCE

FORMULA	CHEMICAL NAME	SOLUBILITY (GM. PER CC. AT 25° C.)	
		In Water	In Alcohol
ZnS.......	Zinc sulfide	Practically insoluble	Insoluble
CaS.......	Calcium sulfide	Slightly soluble	Insoluble
BaS.......	Barium sulfide	Slightly soluble	Insoluble
FeS.......	Ferrous sulfide	Practically insoluble	Insoluble

Zinc sulfide is a white, practically insoluble powder which is one of the ingredients formed in the preparation of White Lotion N.F. The basic reaction between Zinc Sulfate and Sulfurated Potash is as follows:

$$ZnSO_4 + K_2S_5 \rightarrow ZnS + 4S + K_2SO_4$$

White Lotion is used in treating some skin infections. Zinc Sulfide is also used in certain paint pigments.

A form of *calcium sulfide* was included in the U.S.P. IX, under the title of Crude Calcium Sulphide, which contained not less than 55 per cent of CaS. This impure sulfide was a grayish-white or yellowish powder that had an odor of hydrogen sulfide. It has been used as a depilatory and as a parasiticide. The method of preparation depended upon the reduction of calcium sulfate with charcoal and starch by heating a mixture of the three substances to bright redness.

Pure calcium sulfide is a pale yellow (it may also appear as grayish-white) solid with the odor of hydrogen sulfide. It is not soluble in water but slowly hydrolyzes to form the more soluble calcium hydrogen sulfide. It is soluble in aqueous solutions of ammonium compounds.

Barium sulfide is a white, water-insoluble substance which is slowly hydrolyzed to form the more soluble barium hydrogen sulfide and hydrogen sulfide. Barium sulfide is

used as a depilatory chiefly in the form of a paste which is made with starch and water. It is made by the reduction of barium sulfate with carbon at high temperatures.

Barium sulfide is not used for internal administration because it is extremely poisonous, while barium sulfate, a white, water-insoluble, nonpoisonous salt, is frequently prescribed and used in roentgenographic examination of the alimentary canal. The common practice of using abbreviations on prescriptions and negligence on the part of some pharmacists has resulted in the dispensing of barium sulfide in cases where barium sulfate was intended, with consequent serious poisoning and even death of the patient. In some cases the pharmacist has been held negligent and legally liable. To avoid such confusion, the U.S.P. cautions that when barium sulfate is prescribed, the title should always be written out in full.[18]

The sulfides of barium, calcium, and strontium have the peculiar property of glowing or "phosphorescing" after exposure to light. Barium sulfide is known as Bononian Phosphorus and emits an orange-colored light. Calcium sulfide is known as Canton's Phosphorus and emits a white light, as does strontium sulfide.[19]

Ferrous sulfide is available in the form of dark-brown to black cylindrical sticks, lumps and granules. It is insoluble in water. The compound reacts with acids to liberate hydrogen sulfide and form water-soluble iron salts. Its chief use is as a source of hydrogen sulfide.

THE METALLIC PERSULFIDES (POLYSULFIDES)

The persulfides, or the polysulfides as they are commonly known, may be considered as compounds analogous to the peroxides. That is, they are compounds that contain more sulfur than the normal valence of the nonsulfur elements will normally permit. Since the characteristic group of the peroxides is —O—O— and the metallic peroxides are considered to be compounds in which the hydrogen of H_2O_2 is replaced by the metallic ion, the polysulfides are similar; thus, sodium disulfide may be Na—S—S—Na. The polysulfides consist not only of the disulfide, but there are also the tri-, tetra- and pentasulfides, e.g., CaS_2, CaS_3(?), CaS_4(?) and CaS_5. The corresponding acids are produced from solutions of the polysulfides, but the acids are relatively unstable and tend to break down to hydrogen sulfide and sulfur.

The persulfides are prepared by the action of excess sulfur on solutions of metallic hydroxides or of hydrosulfides.

$$M''(OH)_2 + S_x \rightarrow M''S_2 \ldots M''S_5 + M''S_2O_3 + H_2O$$

$$Ca(OH)_2 + S_x \rightarrow CaS_2 \ldots CaS_5 + CaS_2O_3 + H_2O$$

The number of metallic polysulfides of pharmaceutical importance is comparatively limited. Sulfurated Potash N.F.[20] is defined as a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It occurs in irregular pieces that vary in color from a liver-brown to greenish-yellow. The product is unstable when exposed to air and gradually loses its characteristic color. It is soluble in water, 1 gram dissolving in about 2 cc. and forming a light-brown solution. The most common use of Sulfurated Potash, or "Liver of Sulfur" as it is commonly known, is in the preparation of White Lotion N.F.,[21] in which zinc sulfide and free sulfur are obtained as finely suspended precipitates.

Ammonium Polysulfide Test Solution is described in the U.S.P. as "a yellow liquid, made by saturating ammonium T.S. with sulfur." It is primarily used as a reagent in qualitative analysis to dissolve the sulfides of arsenic, antimony and tin.

Another N.F. preparation containing polysulfides is Sulfurated Lime Solution.[22] It is prepared by the action of sulfur on

freshly slaked lime that is suspended in boiling water. The finished product is a clear, orange-colored liquid that is easily decomposed by acids or exposure to air. The preparation is used in the treatment of skin diseases. Preparations of a similar chemical composition are used as contact insecticides, in the control of scale insects, and as fungicides. The preparations for this purpose are known as Lime-Sulfur and are available as a powder, lime-sulfur concentrate, and in proper dilutions for uses under specific conditions.

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9

Hydroxides (Oxyacids) of Group VI and Their Salts of Pharmaceutical Importance

The sixth group of the periodic system contains two subgroups which in some respects differ from each other very markedly. The sulfur subgroup, including sulfur, selenium and tellurium, is characterized by nonmetals, or substances whose oxides combine with water to form acids. The chromium subgroup includes chromium, molybdenum, tungsten and uranium, all of which are regarded as metals. Their oxides should form bases when combined with water. All of the elements of group VI show an electronegative valence of 2 and electropositive valences of 2, 4 and 6. In their lower valence relations, the chromium subgroup elements form the positive part of compounds and they act like metals. However, the valence of 6 is the most typical of the group, and in compounds where this prevails, the elements are parts of the negative ions. Therefore, when the valences are satisfied by hydroxyl groups, the hexahydroxides, tetrahydroxides and dihydroxides can be derived. These, or their partial dehydration products, are the oxygen acids of the elements of the sixth group. They are given in the following table; however, the list does not include all of the known oxyacids of the elements. Moreover, there are salts for which the corresponding acid is not known.

HEXAHYDROXIDES

With $\mathcal{S}$ as the general symbol for the hexavalent elements of the sixth group, the hexahydroxides and their partial and complete dehydration products, along with the names, are tabulated on page 130.

Occurrence. Many of the hexahydroxides and their partial and complete dehydration products are known. The hydroxides do not occur as such, but some are represented in nature in the form of salts. Some of the trioxides of the chromium subgroup are ores of the elements.

The hexahydroxides themselves are not well known. When sulfuric acid is added to water, it combines with the latter with violence and the evolution of much heat to form the monohydrate and the dihydrate. There is also a slight diminution of volume, as evidenced by the increased specific gravity when water is added to 100 per cent H_2SO_4. The rise in temperature and the increase in specific gravity are physical changes accompanying the formation of definite chemical compounds, the hydrates of H_2SO_4, i.e., $H_2SO_4 \cdot H_2O$ and $H_2SO_4 \cdot 2H_2O$, better written as $SO(OH)_4$ or H_4SO_5 and $S(OH)_6$ or H_6SO_6, at low temperatures. When sulfuric acid and water are mixed in

$S(OH)_6$ Hexahydroxide ("-ic" Acid Dihydrate)	$SO(OH)_4$ Monoxide-tetrahydroxide ("-ic" Acid Monohydrate)	$SO_2(OH)_2$ Dioxide-dihydroxide ("-ic" Acid)	SO_3 Trioxide ("-ic" Acid Anhydride)
$S(OH)_6$ Sulfuric acid dihydrate	$SO(OH)_4$ Sulfuric acid monohydrate	* $SO_2(OH)_2$ Sulfuric acid	SO_3 Sulfur trioxide (Sulfuric acid anhydride)
$Se(OH)_6$	$SeO(OH)_4$	$SeO_2(OH)_2$ Selenic acid	SeO_3 Selenium trioxide (Selenic acid anhydride)
$Te(OH)_6$ Orthotelluric acid	$TeO(OH)_4$	$TeO_2(OH)_2$ Telluric acid	TeO_3 Tellurium trioxide (Telluric acid anhydride)
$Cr(OH)_6$	$CrO(OH)_4$	* $CrO_2(OH)_2$ Chromic acid	* CrO_3 Chromium trioxide (Chromic acid anhydride)
$Mo(OH)_6$	$MoO(OH)_4$	* $MoO_2(OH)_2$ Molybdic acid	* MoO_3 Molybdenum trioxide (Molybdic acid anhydride)
$W(OH)_6$	$WO(OH)_4$	$WO_2(OH)_2$ Tungstic acid	WO_3 Tungsten trioxide (Tungstic acid anhydride)
$U(OH)_6$	$UO(OH)_4$	* $UO_2(OH)_2$ Uranic acid	UO_3 Uranium trioxide (Uranic acid anhydride)

* Compounds that are represented in the U.S.P. or N.F., either as such or in the form of their salts.

the proper proportions, i.e., $H_2SO_4 + H_2O$ and $H_2SO_4 + 2H_2O$, these hydrates can be made to crystallize. They are very unstable, however, and readily decompose to H_2SO_4 and H_2O. Orthotelluric acid, $Te(OH)_6$, is believed to be the product resulting from the action of oxidizing agents on TeO_2. The acid is a strong oxidizing agent but it has only weak acidic properties.

The monoxide-tetrahydroxides are known only as intermediates in the formation of the hexahydroxides from the trioxides or in the decomposition of the hexahydroxides. As noted in the table, the dioxide-dihydroxides are known as the "-ic" acids of the elements. These are by far the most common acids, both in the free and the combined states.

Sulfuric acid is employed extensively in reactions conducted on both the laboratory and industrial scales. Except in its diluted form, it has no medicinal value; nevertheless, it is mentioned frequently in the U.S.P. and N.F. It is used in numerous qualitative tests and in the preparation of volumetric solutions. Its salts, including Sodium, Potassium, Barium, Magnesium and Ferric Sulfates and many others are to be found listed in the U.S.P. and N.F.

Chromic acid, H_2CrO_4, is represented in the Pharmacopœia by reagent Potassium Chromate, K_2CrO_4, and the anhydride Chromium Trioxide or Chromic Anhydride.*

Reagent Molybdic Anhydride and Ammonium Molybdate T.S., U.S.P., are derived from molybdic acid, H_2MoO_4.

* An official synonym is "Chromic Acid."

Uranic acid, H_2UO_4, is represented among the U.S.P. reagents by Uranium Acetate (Uranyl Acetate), $UO_2(CH_3COO)_2$.

Methods of Formation and Preparation. Only general methods of formation and preparation will be considered. Since sulfuric acid is the most important of these acids pharmaceutically, its formation and preparation by these methods will be emphasized.

I. HYDRATION OF THE OXIDE.

A. $SO_3 + H_2O \rightarrow H_2SO_4$ or $SO_2(OH)_2$

$SO_3 + 2H_2O \rightarrow H_4SO_5$ or $SO(OH)_4$

$SO_3 + 3H_2O \rightarrow H_6SO_6$ or $S(OH)_6$

Sulfur trioxide has a great affinity for water. It fumes strongly in the air and unites with water with explosive violence and the liberation of much heat, forming the hydroxides, or acids, indicated above; the hydroxide formed depends upon the ratio in which SO_3 and H_2O are mixed. This method is used for the preparation of sulfuric acid from sulfur trioxide which has been prepared by the contact process.*

B. $CrO_3 + H_2O \rightarrow H_2CrO_4$

When Chromium Trioxide is dissolved in water, chromic acid, H_2CrO_4, is undoubtedly formed.[1] This compound has never been isolated because of its instability, water being eliminated with reversion to the anhydride or trioxide.

II. ACTION OF A SUITABLE ACID UPON THE "-ATE" SALT.

A. $Na_2SO_4 + 2HCl \rightarrow 2NaCl + H_2SO_4$

This reaction takes place in the course of the assay of Sodium Sulfate.[2] The sulfuric acid thus produced is precipitated, upon addition of barium chloride, as barium sulfate and weighed as such.

B. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O + 6HNO_3 +$
$7H_2O \rightarrow 7H_2MoO_4 \cdot H_2O + 6NH_4NO_3$

* See Sulfur Trioxide.

In the preparation of Ammonium Molybdate Test Solution,[3] the ammonium molybdate which is formed is treated with strong nitric acid; during this treatment the above reaction occurs. When salts of molybdic acid are treated with nitric acid, the monohydrate of the acid, $H_2MoO_4 \cdot H_2O$, or $MoO(OH)_4$, is formed. Upon isolating and drying, this acid loses water, forming H_2MoO_4.

III. OXIDATION OF ACIDS LESS RICH IN OXYGEN.

A. $H_2SO_3 + O \rightarrow H_2SO_4$

This is the reaction which commonly takes place when sulfurous acid is exposed to the air or when it is used as a reducing agent.

The reaction is also involved in the commercial manufacture of sulfuric acid by the lead chamber process. The following equation illustrates the fundamental reaction of the process:

$$3SO_2 + 2HNO_3 + 2H_2O \rightarrow 3H_2SO_4 + 2NO$$

In addition, there are numerous side reactions, some of which are not clearly understood. By one of these, nitrosyl sulfuric acid is formed:

$$2NO + O_2 \rightarrow 2NO_2$$

$$SO_2 + NO_2 + NO + O_2 + H_2O \rightarrow 2H(NO)SO_4$$

The sulfuric acid produced by this process has a concentration of 60 to 70 per cent and it contains numerous impurities, including oxides of nitrogen, lead, arsenic and iron. It is suited for limited industrial application.

B. $H_2SO_3 + I_2 + H_2O \rightarrow H_2SO_4 + 2HI$

In the assay of sulfurous acid, the oxygen required for oxidizing sulfurous acid to sulfuric acid is produced by the action of iodine on water.[4]

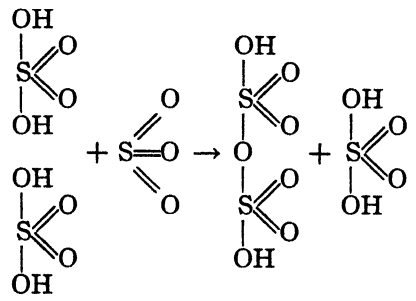
Properties and Uses. The hexahydroxides of this group are unstable, existing for the most part only in solution. Sulfur hexa-

hydroxide, however, can be isolated at low temperatures. Hydrated orthotelluric acid $Te(OH)_6 \cdot 2H_2O$ and $Te(OH)_6 \cdot 4H_2O$ are crystalline solids at about $-5°$ C. The monoxide-tetrahydroxides are more stable. The monoxide-tetrahydroxide of sulfur decomposes at 8° C., that of molybdenum decomposes when dried at room temperatures and that of tungsten when heated. There is no readily apparent relationship among the physical properties of the "-ic" acids of this group. Sulfuric acid is a heavy colorless liquid, while the other acids are solids, with colors ranging from orange-red to yellow.

All of the acids of the type H_2SO_4 have a tendency to lose water when heated and pass over to the trioxide. Under other conditions they readily lose water between two or more molecules to form complex acids. Thus, when concentrated sulfuric acid is treated with sulfur trioxide, a dehydrating agent, water is extracted from two molecules of the acid:

$$2H_2SO_4 + SO_3 \rightarrow H_2S_2O_7 + H_2SO_4$$

Written structurally:



The new acid thus formed, $H_2S_2O_7$, is known as disulfuric acid or pyrosulfuric acid and also as Nordhausen sulfuric acid; it also can be obtained by dissolving two molecules of SO_3 in one of H_2O or by dissolving one molecule of SO_3 in the one of H_2SO_4:

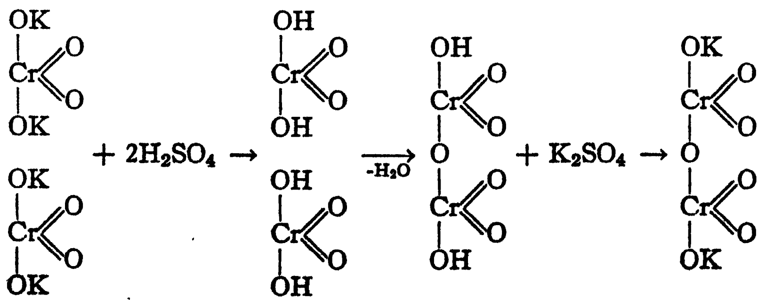
$$2SO_3 + H_2O \rightarrow H_2S_2O_7$$
$$SO_3 + H_2SO_4 \rightarrow H_2S_2O_7$$

Pyrosulfuric acid forms both acid and normal salts, e.g., KHS_2O_7, potassium acid pyrosulfate, and $K_2S_2O_7$, potassium pyrosulfate. Upon exposure to the air, SO_3 escapes from the acid and combines with the moisture of the air, causing dense fumes of H_2SO_4 to hang over the surface of the acid. Therefore, it is usually called fuming sulfuric acid.[5]

In the same way, when concentrated sulfuric acid is added to potassium chromate, chromic acid is formed first; this immediately loses water, forming dichromic acid, which crystallizes out as potassium dichromate (see equation below). Dichromic acid, $H_2Cr_2O_7$, which is analogous to disulfuric acid, also forms normal and acid salts, the best known of which is Potassium Dichromate U.S.P. This compound, which is sometimes called potassium bichromate, should not be confused with potassium acid chromate, $KHCrO_4$, analogous to potassium acid sulfate, $KHSO_4$, also known as potassium bisulfate. The use of Potassium Dichromate as an oxidizing agent has been referred to elsewhere.*

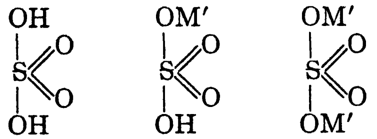
This type of condensation between the "-ic" acid molecules does not necessarily

* See Halogens, Methods of Formation and Preparation, pp. 23-32; also Oxygen, Methods of Formation and Preparation, pp. 92-99.



stop with the union of two molecules but may continue, with the formation of complex acids. Molybdic acid shows a strong tendency in this direction, forming compounds like ammonium molybdate, for example, $(NH_4)_6Mo_7O_{24}$, which is the ammonium salt of an acid formed by seven molecules of molybdic acid condensing in such a way that a hexabasic acid is formed. Tungstic acid is also prone to undergo complex condensations, forming polytungstates, such as $Na_{10}W_{12}O_{41} \cdot 28H_2O$, etc.

All of the "-ic" acids of the elements of the sixth group have two hydrogens which are replaceable by metals, hence they form two types of salts, commonly called the "acid-ates" when one hydrogen is replaced and "normal-ates" or neutral salts when both hydrogens are replaced by a metal. This may be summarized in the following way when S stands for these hexavalent elements:



"-ic Acid" "Acid -ate" "Normal -ate"

Thus, there may be both acid and normal sulfates, selenates, tellurates, chromates, molybdates, tungstates and uranates. For sulfuric acid, these salts are well known, as they are also for selenic and telluric acids, but for the members of the other subgroup, the salts are not common and there are few of pharmaceutical interest. The bisulfate ion, HSO_4^-, and the sulfate ion, SO_4^{--}, are not especially active from the therapeutic standpoint. However, it may be well to point out generally that the bisulfates and the sulfates are stable compounds. All of them, with the exception of the sulfates of the alkaline earth metals and a few odd compounds like silver sulfate, are soluble in water. The sulfates of the trivalent metals like aluminum and iron yield strongly acidic solutions due to the partial hydrolysis of the compounds.

The acidic character of the "-ic" acids of the elements of this group decreases with an increase in the atomic weight of the element concerned. This corresponds closely with the fact that the elements become decidedly metallic in character with an increase in the atomic weight. Thus, sulfur, selenium and tellurium are definitely nonmetallic in character, and their acids, sulfuric, selenic and telluric acids, are strong acids; on the other hand, the elements of the other subgroup are distinctly metallic, and uranium is both acid and base-forming. Thus, toward strong and even weak acids uranic acid acts as a base, forming uranyl salts like uranyl sulfate, uranyl nitrate and uranyl acetate.

Sulfuric acid has a great affinity for water, combining with it in the free state with the evolution of much heat. Therefore, when water and sulfuric acid are mixed, it should be done carefully and the acid should always be poured into the water. In this way, the acid, being heavier than the water, will pass down through the water, dissolving as it goes through the entire quantity of water. If, on the other hand, the water is poured into the acid, the water will remain on top, coming into contact only at the surface of the acid. The heat of solution, therefore, will be generated and concentrated in one place and will become so great that the water may boil at the line of contact, spattering the acid and causing severe burns and other damage.

Because of its great affinity for water, sulfuric acid is a strong dehydrating agent. It will extract water from other acids, as shown in the case of chromic acid, and from organic and other inorganic compounds, as well as combining with water in the free state. Sulfuric acid is used as a dehydrating agent in pharmacy in a variety of ways, some of which may be summarized as follows:

1. As a drying agent—Many examples of this use of sulfuric acid are found in the U.S.P. and N.F., especially where chemicals and other substances are dried to constant

weight over sulfuric acid before being assayed.*

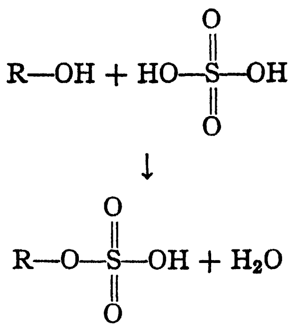
2. For the removal of water in condensation reactions—This is a common reaction in organic chemistry; sulfuric acid is used to take up the water liberated during the condensation. When preparing methyl salicylate or Wintergreen Oil, a small quantity of sulfuric acid is used to take up the water formed in the condensation of methyl alcohol and salicylic acid. The same reaction takes place in the preparation of the U.S.P. Pyroxylin.[6]

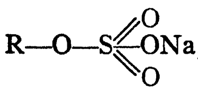
3. As a test for readily carbonizable substances—Many organic substances, especially those of a carbohydrate nature (i.e., which contain hydrogen and oxygen in the proportion in which they unite to form water), give up a large part of these elements in the form of water when treated with concentrated sulfuric acid and become charred or carbonized. The presence of such substances as impurities in other substances which do not behave in the same way can be detected by treatment with concentrated sulfuric acid. Substances treated in this way for "carbonizable impurities" are numerous in the U.S.P. and N.F.[7]

4. As a test for substances which produce more or less characteristic color reactions when subjected to the action of sulfuric acid—This may be used either as a test for identity or impurity.[8]

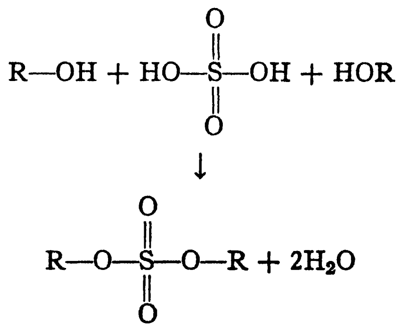
5. It is used as a test for substances which yield more or less characteristic odors when subjected to the dehydration action of sulfuric acid.[9]

Sulfuric acid combines not only with water but also with low molecular weight alcohols with the evolution of much heat. The acid will react with one or two molecules of alcohol, depending upon the conditions observed. With one mole of acid and one mole of alcohol, the alkyl acid sulfates are formed:



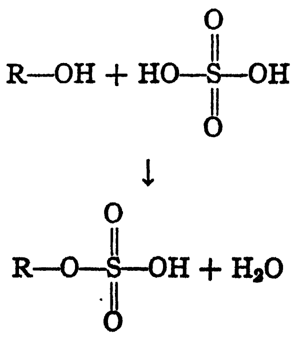
The acid sulfates of high molecular weight alcohols (C_{12} to C_{18}) are converted into water-soluble salts, yielding compounds which have unusual detergent properties. They are of the general formula , and are active in acid, alkaline and hard waters. Dreft, Irium and Gardinol are illustrations. Sodium Lauryl Sulfate U.S.P.[10] is the official representative of the alkyl sulfates.

With two moles of alcohol and one of acid, the normal sulfate may be formed along with the simple ether:

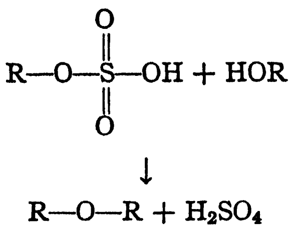


(R_2SO_4)

and



* See for example under assays of Ammonium Benzoate, Silver Nitrate, Arsenic Tri-iodide and countless others in the U.S.P. and N.F.



Dimethyl sulfate, $(CH_8)_2SO_4$, is a typical normal alkyl sulfate. It is a powerful reagent whose great affinity for water is illustrated in its use in preparing methyl esters and methyl ethers.

The "-ic" acids of this group act as fairly strong oxidizing agents, especially sulfuric, selenic and telluric acids. Sulfuric acid is not ordinarily considered as an oxidizing agent, yet when used with reducing agents, it acts as one. An example is the use of sulfuric acid and carbon for the preparation of sulfurous acid and sulfur dioxide:

$$H_2SO_4 + C \xrightarrow{\Delta} H_2SO_3 + CO$$

We say that carbon reduces the sulfuric acid to sulfurous acid, but it is just as correct to say that the sulfuric acid oxidizes carbon to carbon monoxide and the acid itself is reduced in the process. Again, when potassium or sodium iodide is treated with concentrated sulfuric acid, hydriodic acid is formed first:

$$H_2SO_4 + 2KI \rightarrow K_2SO_4 + 2HI$$

The HI formed reacts with more sulfuric acid:

$$H_2SO_4 + 2HI \rightarrow H_2SO_3 + H_2O + I_2$$

The brownish color of iodine will appear at once, and the odor of sulfurous acid will become apparent, the former caused by the oxidation of hydriodic acid and the latter by reduction of sulfuric acid. The reaction may not stop here.* It is to prevent such reactions as these that the U.S.P. and N.F. specify that dilute sulfuric acid be used in testing the iodides and bromides for impurity.† Also, whenever potassium iodide is used for the production of hydriodic acid in assay processes, the use of dilute sulfuric acid is preferred.

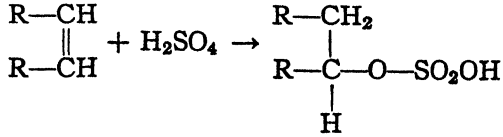
Another example of the oxidizing property of sulfuric acid is found in its use to dissolve many metals. These metals are oxidized to the corresponding sulfates, while a part of the sulfuric acid is reduced to sulfurous acid:

$$Cu + 2H_2SO_4 \rightarrow CuSO_4 + SO_2 + 2H_2O$$

Chromic acid is also a strong oxidizing agent and is used as such. Examples of its use in this capacity have already been mentioned in connection with potassium dichromate. A solution of chromic acid has often been used for oxidizing primary alcohols to aldehydes and secondary alcohols to ketones. An example of this is found in the test for identity of Salicin in the N.F.[11]

Thus far, the properties of the "-ic" acids described have been based upon their hydration and dehydration, upon their oxidation and reduction, upon reactions in which they act as condensing agents and upon the formation of salts of both the inorganic and organic types. Sulfuric acid undergoes several unusual reactions with organic compounds; many of these reactions are of great importance in the field of pharmacy.

When an unsaturated hydrocarbon, alcohol, acid, ester, etc., is treated with strong sulfuric acid, the acid adds on at the point of unsaturation, yielding a secondary or tertiary alkyl sulfate, as the case may be. For example:



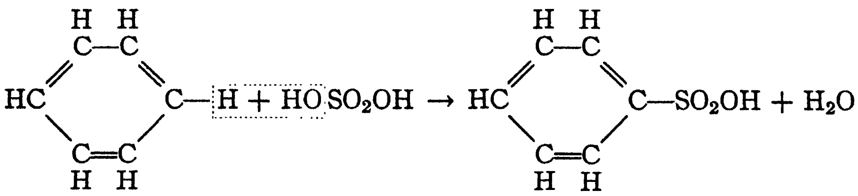
The secondary and tertiary alkyl sulfates are regarded superior to the primary alkyl sulfates as wetting agents. It is assumed that when their salts are dissolved in water,

* For other reactions occurring see page 43.

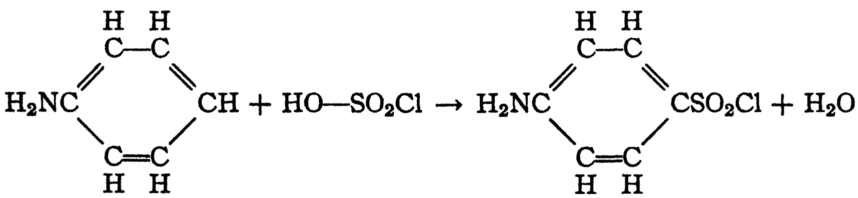
† See test for impurity under the U.S.P. iodides and bromides where sulfuric acid is called for.

hydrates which reduce the surface tension of the water are formed. Usually, the presence of a wetting agent greatly enhances the properties of antiseptics because the solution of the medicament diffuses through membranes at a greater rate when its surface tension is reduced.

Because it is an acid, one would expect sulfuric acid to always function as a source of hydrogen ions. The reaction between strong sulfuric acid and benzene represents a notable exception.



In this case, the benzene serves as the source of hydrogen. While this serves as a means of preparing benzene sulfonic acid and other aromatic sulfonic acids, the reaction is not efficient. Thus, in preparing the sulfa drugs, extensive use is made of chlorosulfonic acid as a sulfonating agent. It is an extremely active chemical and must be employed with great caution.



Aniline — Aniline *p*-Chlorsulfonate

The conversion of the chlorosulfonate to the amide (sulfanilamide) or to the free acid is an easy matter.

Because it can combine with insoluble basic nitrogen compounds to form water-soluble salts, sulfuric acid is used extensively in converting alkaloids like morphine, quinine and strychnine into the corresponding sulfates, according to the reaction.

$$2(R—NH_2) + H_2SO_4 \rightarrow (R—NH_2)_2 \cdot H_2SO_4$$

Another unusual reaction of the "-ic" acids results when molybdic or tungstic acid is brought into contact with phosphoric acid just as happens when nitric acid is added to a solution of ammonium molybdate and a soluble phosphate. A complex phosphomolybdic or phosphotungstic acid is formed. Little is known of the structure of these acids, but they form beautiful crystals and appear to be definite chemical compounds.[12] They form insoluble salts with potassium, ammonium and with many alkaloids and are important pharmaceutically as reagents for the detection of alkaloids.

Salts of the Acids

Few of the acids derived by the partial dehydration of the hexahydroxides are represented by salts. Most common among these acids is sulfuric acid, which, being di-protic, yields two series of salts, namely, the acid sulfates and the normal sulfates. They have no therapeutic value, but the bisulfates represented among the reagents of the N.F. are sodium bisulfate and potassium bisulfate. The latter is used in the identification of glycerol which, when heated with potassium bisulfate, yields acrylic aldehyde or acrolein.

The normal salts of sulfuric acid are very common.

Sodium Sulfate is official in the U.S.P.[13] as the decahydrate (Glauber's Salt, $Na_2SO_4 \cdot 10H_2O$). It is an efficient diuretic and hydragogue cathartic. To render it more

palatable, it can be exsiccated and made into an effervescent powder. Anhydrous sodium sulfate is used to dry nonaqueous solutions of organic compounds.

Ammonium sulfate no longer is used as a therapeutic agent, but because it is a strong electrolyte, it is used in pharmaceutical manufacturing processes as a protein precipitant. In this capacity, it is employed on a large scale in the fractionation of blood plasma and water-soluble hormones.

Cupric Sulfate U.S.P. ($CuSO_4 \cdot 5H_2O$) is used therapeutically as an antiseptic and fungicide. It is recommended as a chemical antidote in phosphorus poisoning, copper phosphide being formed in the reaction. Fehling's and Benedict's solutions represent alkaline solutions of copper sulfate which are used in testing both qualitatively and quantitatively for the presence of reducing substances like aldehydes, certain ketones and reducing sugars. Dilute solutions of the compound are used as standards in colorimetric determinations.[14] Copper sulfate is prepared by the action of sulfuric acid on copper in the presence of concentrated nitric acid:

$$Cu + 4HNO_3 \rightarrow Cu(NO_3)_2 + 2NO_2 + 2H_2O$$

$$Cu(NO_3)_2 + H_2SO_4 \rightarrow CuSO_4 + 2HNO_3$$

Other methods include the roasting of cupric sulfide and the oxidation of copper in the presence of sulfuric acid.

The therapeutic properties of **Magnesium Sulfate** have been recognized for a long time. Perhaps it is best known as Epsom Salts, a name derived from Epsom, England, where the chemical was found in spring water. Through osmotic retention, it causes large volumes of water to accumulate in the intestine, accounting for its cathartic properties. Also due to its osmotic influence, $MgSO_4 \cdot 7H_2O$ is employed as a local remedy indicated in inflammatory conditions, sprains, bruises, etc. When injected intravenously, it manifests the anticonvulsant action characteristic of the magnesium ion. The heptahydrate is official in the U.S.P., and the sterile solution, in ampule form, is official in the N.F.[15]

Calcium Sulfate ($CaSO_4 \cdot 2H_2O$) is listed among the U.S.P. reagents and test solutions. Plaster of paris ($CaSO_4 \cdot \frac{1}{2}H_2O$) is employed extensively in orthopedic practice. When mixed with three-fifths of its weight of water, the hemi-hydrate expands and solidifies, forming a cementlike mass of calcium sulfate dihydrate. In this capacity it is employed to provide mechanical support in the form of casts for the immobilization of various parts of the body.

Because of its optical density, **Barium Sulfate** is used in the fluoroscopic and x-ray examinations of the gastro-intestinal tract. Being virtually insoluble in water (2.3 mg/100 cc. at 18° C.), the compound is harmless and is administered orally and rectally in doses up to 100 Gm. Soluble salts of barium, however, are extremely poisonous for humans and it is important that barium sulfate for medicinal use be free from soluble barium salts. This limits the method of preparation to one of metathesis, e.g.,

$$BaCl_2 + M'_2SO_4 \rightarrow BaSO_4 + 2M'Cl$$

The precipitate of barium sulfate is readily washed free of unreacted barium chloride.

Barium sulfate for industrial purposes is prepared by roasting the sulfide, consequently the final product may contain unreacted barium sulfide and barium sulfite.

To guard against poisoning through misinterpretation, the Pharmacopœia warns against the use of the abbreviation, "Bar. Sulf."[16]

Zinc Sulfate of medicinal quality ($ZnSO_4 \cdot 7H_2O$) is prepared by the action of dilute sulfuric acid on metallic zinc. White Vitriol of commerce contains three molecules of water of crystallization. Zinc Sulfate U.S.P. is poisonous, causing violent vomiting and incessant retching when taken in overdose. When administered properly,

it serves well as an emetic. It is an astringent and antiseptic, and the dilute solution prepared from Compound Zinc Sulfate Powder [17] is used as a vaginal douche.

Aluminum Sulfate is closely related to the alums (p. 235). It can be prepared readily by the action of sulfuric acid on aluminum hydroxide. The compound $[Al_2(SO_4)_3 \cdot 18H_2O]$ is used therapeutically as a styptic and mild antiseptic.

Medicinal Ferrous Sulfate $(FeSO_4 \cdot 7H_2O)$ is prepared by treating iron with sulfuric acid. The salt is official in the Pharmacopœia as such and in the exsiccated form which is used in the manufacture of capsules and tablets for the treatment of anemia. Ferrous Sulfate Syrup N.F. represents another form of the medicament.

Because of its high acidity, **ferric sulfate** is not used medicinally, though it is one of the U.S.P. reagents. The 10 per cent solution, known as Iron Tersulfate Solution and as Ferric Sulfate Solution, was used in preparing freshly precipitated ferric hydroxide, the former official arsenic antidote.[18]

$$Fe_2(SO_4)_3 + 3Mg(OH)_2 \rightarrow 2Fe(OH)_3 + 3MgSO_4$$

Ferric Subsulfate Solution,[19] also called Monsel's Solution, is a powerful styptic. In its preparation the following reaction is believed to occur:

$$12FeSO_4 + 3H_2SO_4 + 4HNO_3 \rightarrow 3FeO(SO_4)_5 + 4NO + 5H_2O$$

TRIOXIDES

The trioxides have already been noted under the table of the hexahydroxides of these elements and they represent the complete dehydration products of the hexahydroxides. The most important trioxides in pharmacy are sulfur trioxide, chromium trioxide and molybdenum trioxide.

Occurrence. The occurrence of these trioxides in nature is rare. The trioxides of molybdenum, uranium and tungsten, however, do occur with other oxides in certain ores.

In the U.S.P. and N.F., sulfur trioxide does not occur as such but is contained along with H_2SO_4 in Fuming Sulfuric Acid. Chromium Trioxide, or Chromic Anhydride, CrO_3 is described in a U.S.P. monograph, and molybdenum trioxide, MoO_3, is listed among the reagents under the name of Molybdic Anhydride or Molybdic Acid.

Methods of Formation and Preparation.

I. Oxidation of the Dioxide.

$$SO_2 + \tfrac{1}{2}O_2 \rightarrow SO_3$$

When sulfur is heated in the air, it burns to SO_2 and this oxidizes very slowly to SO_3. This oxidation to SO_3 occurs much more readily in the presence of a catalyst such as platinum. This reaction forms the basis of the catalytic "contact process" for the preparation of sulfuric acid.

SO_2 in solution is slowly oxidized by contact with air to the trioxide. This reaction occurs with sulfurous acid and its salts, the sulfites and bisulfites; the air oxidizes them to sulfuric acid, sulfates or bisulfates, respectively.

II. Dehydration of the Corresponding "-ic" Acid.

A. $H_2SO_4 \xrightarrow{\Delta} H_2O + SO_3$

When sulfuric acid is heated strongly, it is dehydrated and gives off dense white fumes of SO_3.

B. $H_2CrO_4 \rightarrow H_2O + CrO_3$

or

$$H_2Cr_2O_7 \rightarrow H_2O + 2CrO_3$$

This is the method used for preparing Chromium Trioxide U.S.P. When potassium chromate, K_2CrO_4, is treated with concentrated sulfuric acid two molecules react, forming dichromic acid, $H_2Cr_2O_7$. This compound, with more sulfuric acid, is dehydrated to chromium trioxide. The chromium trioxide separates out as deep-red

crystals. In the preparation of the familiar "cleaning solution" used in laboratories for the cleaning of burettes, pipettes and other glassware, the same reaction takes place. Concentrated sulfuric acid is added to a saturated solution of sodium or potassium dichromate. A saturated solution of chromic acid, from which CrO_3 separates, is the result. The solution is an excellent oxidizing agent and is widely used for cleaning volumetric glassware.

III. Heating the Corresponding "-ate" Salt. Many of the metallic sulfates yield SO_3 upon heating:

$$FeSO_4 \cdot 7H_2O \xrightarrow{\Delta} 7H_2O + FeO + SO_3$$

$$Fe_2(SO_4)_3 \xrightarrow{\Delta} Fe_2O_3 + 3SO_3$$

$$MgSO_4 \cdot 7H_2O \xrightarrow{\Delta} 7H_2O + MgO + SO_3$$

etc.

Properties and Uses. The trioxides of the sixth group are all solids at low temperatures. Sulfur trioxide liquefies at 15° C. and boils at 44.8° C. The other trioxides are solid at ordinary temperature.

All of the trioxides unite with water to form the corresponding "-ic" acids. The acid character of the trioxides decreases with an increase in the atomic weight of the element. Thus, sulfur trioxide, SO_3, is the most strongly acidic trioxide, and UO_3, the oxide of the heaviest metal of the group, is acid toward alkaline hydroxides and basic toward acids. Thus, it forms ammonium uranate on the one hand and uranyl nitrate on the other. It even forms a salt with so weak an acid as acetic acid. This decreasing acidity or increasing basicity among the oxides of the elements of this group corresponds with the change from a nonmetallic to a metallic character with an increase in the atomic weight of the elements themselves.

The trioxides, like their corresponding "-ic" acids, are strong oxidizing agents, being themselves reduced in the process of oxidation to lower oxides. The oxidizing power of SO_3, which exists in solution as H_2SO_4, has already been mentioned (p. 135). Chromium trioxide is used commonly as an oxidizing agent, as are also the chromates and dichromates, and when brought in contact with organic substances it oxidizes them so violently that serious accidents sometimes result. It is destructive to animal and vegetable tissues and should not be allowed to come in contact with the clothing or any part of the body.[20] Chromium trioxide is used as an antiseptic, e.g., in Vincent's angina, as well as for the removal of skin growths such as warts.

TETRAHYDROXIDES

With Ꞩ as the general symbol for the tetravalent elements of the sixth group, the following tetrahydroxides and their partial and complete dehydration products, along with the names, are indicated below:

Ꞩ(OH)$_4$ Tetra-hydroxide	ꞨO(OH)$_2$ Monoxide-Dihydroxide ("-ous" Acid)	ꞨO$_2$ Dioxide ("-ous" Acid Anhydride)
$S(OH)_4$	* $SO(OH)_2$ Sulfurous acid	SO_2 Sulfur dioxide (Sulfurous acid anhydride)
$Se(OH)_4$	* $SeO(OH)_2$ Selenious acid	SeO_2 Selenium dioxide
$Te(OH)_4$	$TeO(OH)_2$ Tellurous acid	TeO_2 Tellurium dioxide

* Compounds that are represented in the U.S.P. or N.F., either as such or in the form of their salts.

It will be noted that in this table the elements of the chromium subgroup have not been included because they seldom function as tetravalent elements, and even when they do, their hydroxides are not commonly known. The dioxides of some of them, i.e., of molybdenum, tungsten and uranium, are known, but are of no significance pharmaceutically.

Occurrence. Of these tetrahydroxides and their partial dehydration products,

only two, sulfurous acid, $SO(OH)_2$, and selenious acid, $SeO(OH)_2$, are of pharmaceutical importance. The tetrahydroxides themselves are unknown.

Sulfurous Acid is recognized in the U.S.P. along with its two sodium salts, Sodium Bisulfite and Exsiccated Sodium Sulfite. Selenious Acid is also recognized in the U.S.P., all four of these products being included among the U.S.P. Reagents.

Methods of Formation and Preparation.

I. Action of Water upon the Dioxide (Hydration).

A. $SO_2 + H_2O \rightarrow H_2SO_3$

Sulfurous acid is formed by passing SO_2 into water, where it dissolves, forming H_2SO_3. The combination thus effected is unstable, however, and H_2SO_3 has never been isolated as such. Upon boiling, the solution acts like a solution of SO_2 in water and all of the SO_2 may be driven off. The solution, however, acts as a dibasic acid, and when treated with alkalies, it forms acid sulfites and normal, or neutral, sulfites.

B. $SeO_2 + H_2O \rightarrow H_2SeO_3$

Selenious acid may be formed by the union of selenium dioxide and water. This acid is a crystalline compound[21] which is also unstable, decomposing under the action of heat to form water and the dioxide.

II. Action of an Acid upon an "-ite" or an "Acid-ite" Salt.

A. $Na_2SO_3 + 2HCl \rightarrow 2NaCl + H_2SO_3$

B. $NaHSO_3 + HCl \rightarrow NaCl + H_2SO_3$

When a metallic sulfite or acid sulfite in solution is treated with an acid, sulfurous acid is formed, a part of which is immediately broken up to form sulfur dioxide, recognized by its pungent odor.[22]

III. Reduction of the Corresponding "-ic" Acid.

A. $H_2SO_4 + C \xrightarrow{\Delta} H_2SO_3 + CO$

One of the common methods for preparing sulfur dioxide in the laboratory is to heat concentrated sulfuric acid with carbon. The sulfurous acid first formed breaks down immediately, with the formation of sulfur dioxide and water.

B. $2H_2SO_4 + S \xrightarrow{\Delta} 2H_2SO_3 + SO_2$

Sulfur dioxide is also obtained by heating concentrated sulfuric acid with sulfur. The sulfurous acid formed breaks down to yield more sulfur dioxide:

$$2H_2SO_3 \rightarrow 2SO_2 + 2H_2O$$

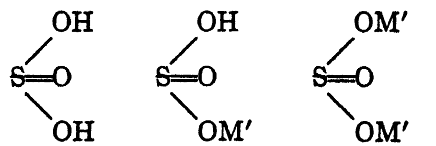
C. $2H_2SO_4 + Cu \rightarrow$

$$CuSO_4 + H_2O + H_2SO_3$$

When concentrated sulfuric acid is used to dissolve certain heavy metals, a part of the sulfuric acid is reduced to sulfurous acid, which further decomposes into sulfur dioxide and water.

Properties and Uses. The properties and uses of the "-ous" acids of the sixth group are almost identical with those of the dioxides, to which these acids are easily dehydrated. Sulfurous acid is a rather weak acid, resembling carbonic acid in strength.

Like the "-ic" acids of this group, the "-ous" acids are dibasic and have two replaceable hydrogens; hence they are capable of forming two types of salts, the acid salts and normal salts. The salts of these "-ous" acids are known as "acid-ites" and normal "-ites," and their formulae may be represented as follows, using the general symbol:



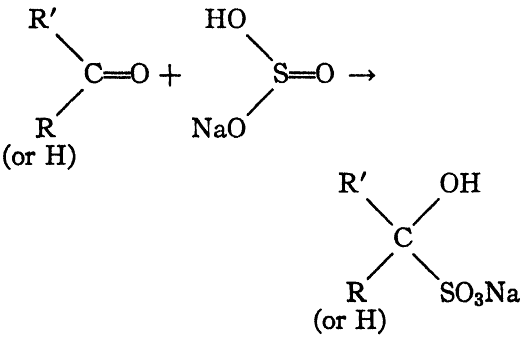
"-ous" Acid   "Acid -ite"   "Normal -ite"

The salts usually are formed by the neutralization of the "ous" acid with the corresponding metallic hydroxide or carbonate. The acid and normal sulfites and selenites of

the alkali metals are soluble in water, while those of the heavy metals are insoluble.

Metallic sulfites are used widely in the pulp and paper industry because of their action upon wood. They digest the wood, separating and bleaching the fibers. Metallic selenites are very toxic to both animal and vegetable organisms. Their use as insecticides in fruit orchards is hampered by the fact that their toxicity causes damage to the growing plants.

As a qualitative reagent, sodium acid sulfite is widely used in organic chemistry for the detection of aldehydes and certain ketones.[23] Both the acid sulfite and the normal sulfite are used as quantitative reagents in the assays of some of the aldehyde and ketone-containing volatile oils of the U.S.P. and N.F. In these reactions, the doubly bound oxygen of the aldehyde or ketone exhibits additive capacity and adds on a molecule of sodium acid sulfite to form a soluble compound:



This type of reaction occurs in the U.S.P. assays for cinnamic aldehyde in Cinnamon Oil, for carvone in Spearmint Oil and in the N.F. assay for carvone in Caraway Oil.[24] In these assays, a solution of the neutral sodium sulfite is used instead of the acid sulfite. In such an instance the presence of the aldehyde or ketone induces the hydrolysis of the sodium sulfite in solution,

$$Na_2SO_3 + HOH \rightarrow NaHSO_3 + NaOH$$

in order that it may add on the sodium acid sulfite thus formed. The addition product with the aldehyde or ketone is formed slowly and remains in solution. This reaction proceeds, with the formation of the addition compound and NaOH, until the solution becomes alkaline in reaction and a state of equilibrium is established among the substances in solution. The NaOH which has been produced then is neutralized by the careful addition of sodium bisulfite solution:

$$NaHSO_3 + NaOH \rightarrow Na_2SO_3 + H_2O$$

This disturbs the equilibrium, and the reaction proceeds as before until it again becomes alkaline and a state of equilibrium is reached again. The neutralization is repeated, and so on, until the mixture no longer becomes alkaline after being heated in a boiling water bath. The fact that the mixture no longer becomes alkaline shows that all of the aldehyde or ketone has gone into combination and therefore the hydrolysis of sodium sulfite is no longer induced. Since the aldehyde or ketone addition product remains in solution, the volume of the residual oil will indicate the difference between the volume of aldehyde or ketone and the volume of the original oil.

The solubilizing effect of sodium bisulfite is illustrated further by Menadione Sodium Bisulfite.[25] When not well-tolerated orally, menadione in oil was injected intramuscularly. Being readily soluble in water, the bisulfite addition product represents a form of menadione which can be injected intravenously to facilitate the coagulation of the blood.

Exsiccated sodium sulfite (Na_2SO_3) is used as a preservative for tannic acid ointment and glycerite.[26] The anhydrous form is preferred for these preparations because the presence of water hastens the decomposition of tannic acid.

DIOXIDES

Occurrence. Sulfur dioxide, SO_2, is the only dioxide of this group of pharmaceutical

importance. It occurs in certain volcanic gases and in the products of combustion of sulfur-containing substances. The air in metropolitan areas, for example, contains SO_2 which has been produced by the combustion of the sulfur compounds contained in coal. Sulfur dioxide is not official as such in the U.S.P. or N.F., but is present in aqueous solution in not less than 6 per cent concentration in Sulfurous Acid U.S.P. Reagents. It is also formed in several tests and assays of the U.S.P. and N.F.

Methods of Formation and Preparation.

I. Direct Union of the Elements.

$$S + O_2 \xrightarrow{\Delta} SO_2$$

Sulfur, when burned in the air, is converted into sulfur dioxide. This is used as a test for identity of sulfur [27] and is also one of the common methods for preparing sulfur dioxide which is used for preparing sulfuric acid by the "contact process."

II. Dehydration of the Corresponding "-ous" Acid.

A. $$H_2SO_4 + C \xrightarrow{\Delta} CO + (H_2SO_3) \rightarrow H_2O + SO_2$$

This is one of the common methods of preparation of sulfurous acid and sulfur dioxide in the laboratory. The sulfurous acid, formed by the reduction of sulfuric acid, is easily dehydrated upon heating to yield sulfur dioxide gas. In fact, any method of formation or preparation of sulfurous acid is also a method for preparing the dioxide because of the ease of dehydration of the acid (p. 140).

B. A similar reaction occurs in the production of SO_2 by heating Sulfonmethane (Sulfonal) and Sulfonethyl-methane (Trional), in which sulfur is present in the same valence as in sulfuric acid. When either compound is heated above its melting point, it is decomposed, the organic part of the molecule is charred, producing carbon, which reduces the sulfuric acid portion of the molecule to SO_2.[28]

III. Action of an Acid upon the Corresponding "-ite" or "Acid-ite" Salt.

A. $$Na_2SO_3 + 2HCl \rightarrow 2NaCl + (H_2SO_3) \rightarrow H_2O + SO_2$$

B. $$NaHSO_3 + HCl \rightarrow NaCl + (H_2SO_3) \rightarrow H_2O + SO_2$$

These reactions have already been referred to under sulfurous acid; they are encountered in tests for identity.

IV. Action of an Acid upon a Thiosulfate.

A. $$Na_2S_2O_3 + 2HCl \rightarrow 2NaCl + (H_2S_2O_3) \rightarrow H_2O + S + SO_2$$

This reaction takes place whenever a metallic thiosulfate is acted upon by hydrochloric acid and is used as a test for identifying thiosulfates.[29]

Even so weak an acid as carbonic acid will bring about the above decomposition. Hence the standard solutions of sodium thiosulfate must be protected from the CO_2 of the atmosphere and must be restandardized frequently.

$$Na_2S_2O_3 + H_2CO_3 \rightarrow Na_2CO_3 + (H_2S_2O_3) \rightarrow H_2O + S + SO_2$$

Properties and Uses. Sulfur dioxide is a colorless gas possessing a characteristic penetrating and suffocating odor. Selenium dioxide is a white solid, of characteristic odor, which volatilizes, without melting, to a yellowish gas. Sulfur dioxide is easily liquefied at ordinary temperatures and the commercial article is usually sold in the liquid form, contained in metal cylinders.

The dioxides combine with water to form the corresponding "-ous" acids. They are the "-ous" acid anhydrides. As mentioned before, these "-ous" acids are not very stable,

and sulfurous acid has not been isolated as such, but it behaves as a dibasic acid.

The dioxides combine with oxygen to form the corresponding trioxides. This reaction takes place in the presence of water to form the corresponding "-ic" acids:

$$2SO_2 + O_2 + 2H_2O \rightarrow 2H_2SO_4$$

This explains why Sulfurous Acid, Selenious Acid, Sodium Bisulfite and Sodium Sulfite are so unstable.

Also, because of the ease with which the above reaction takes place, the dioxides, their corresponding "-ous" acids and the salts of these acids are good reducing agents. Examples of the reducing action of SO_2 are found in the assays of Sulfurous Acid, Sodium Bisulfite and Exsiccated Sodium Sulfite.

The reducing property of SO_2 is also utilized in the test for SO_2 impurity in the U.S.P. Gelatin.[30] In the manufacture of gelatin, especially for capsules, where a perfectly colorless substance is required, sulfur dioxide is used as a bleaching agent. In the U.S.P. test the SO_2 is liberated from its combination by treatment with phosphoric acid. Sodium bicarbonate is added to produce CO_2, which expels the air from the container, thus preventing premature oxidation of the SO_2. The mixture is then distilled and the distillate, containing the SO_2, is collected under the surface of N/10 iodine solution. The following reactions then take place, with the oxidation of SO_2 to H_2SO_4; the SO_4 ion is precipitated as $BaSO_4$, which is collected on a filter, ignited and weighed.

$$2I_2 + 2H_2O \rightarrow 4HI + O_2$$

$$2H_2SO_3 + O_2 \rightarrow 2H_2SO_4$$

$$BaCl_2 + H_2SO_4 \xrightarrow{\bullet} BaSO_4 + 2HCl$$

Sulfur dioxide, or sulfurous acid, acts upon many organic coloring matters, changing them into colorless compounds. The reactions involved are not fully understood. In some instances the bleaching property is undoubtedly due to the reducing action of the acid; the acid takes oxygen from the pigment to render it colorless and is oxidized to sulfuric acid. In other cases, SO_2 or H_2SO_3 apparently adds on to the colored compound, forming a more or less stable, colorless compound. The gradual breaking down of these addition compounds with the restoration of the original color would account for the fact that frequently substances bleached with SO_2 slowly regain their color.

At any rate, sulfur dioxide, sulfurous acid and the sulfites are used for bleaching gelatin, paper, straw goods, silk and woolen textiles, dried fruits, wood pulp and other substances, the texture of which would be injured by a more powerful bleaching agent such as chlorine. In addition, sulfurous acid and the sulfites have a toxic action upon bacterial organisms and are used as fungicides, disinfectants and preservatives in foods and beverages. Sulfites and bisulfites also find some use as anti-oxidants because of their ease of oxidation. Thus, Epinephrine Solution usually contains 0.1 per cent of sodium bisulfite as a preservative.

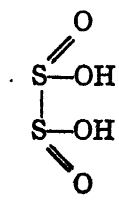
OTHER OXYACIDS OF SULFUR

Several acids of this group other than the "-ous" and "-ic" acids are of interest. Chief among these are hyposulfurous acid and the thio-acids, i.e., acids in which sulfur takes the place of oxygen.

Hyposulfurous acid has never been isolated in the free state but it is known in the form of its salts. It might be regarded as the hydration product of sulfur sesquioxide.

$$H_2O + S_2O_3 \rightarrow H_2S_2O_4$$

Its structural formula can be arranged as follows, showing tetravalent sulfur.

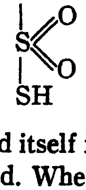


This configuration is in agreement with the marked reducing properties of salts of the acid. The sodium salt is prepared by the action of metallic zinc on an aqueous solution of sodium bisulfite. Sodium hyposulfite (not to be confused with $Na_2S_2O_3$) is used commercially by textile workers to reduce vat dyes and in certain bleaching operations.

THIOSULFURIC ACID AND THIOSULFATES

Sulfur, since it is closest to oxygen in the sixth group of the periodic system, resembles oxygen in its chemical properties and frequently functions in the same way in chemical compounds. Because of this similarity in chemical properties, sulfur frequently can replace oxygen in many compounds. Examples of this sort are found commonly among such organic compounds as thioalcohols, thio-ethers, etc., and also in inorganic compounds, such as in the thio-acids of the fifth group and their salts, for example, thio-arsenous acid, ammonium thioarsenite, etc.

In the same way, sulfur frequently takes the place of oxygen in the acids and salts of the sixth group, especially in connection with the sulfur-containing acids. Thiosulfuric acid, then, may be considered as sulfuric acid in which one of the hydroxyl oxygens has been replaced by sulfur. It has the formula $H_2S_2O_3$ and may be represented by the structure



Thiosulfuric acid itself is unstable and has never been isolated. Whenever it is formed in solution it breaks down at once:

$$H_2S_2O_3 \rightarrow SO_2 + H_2O + S$$

Its salts, however, are stable, and sodium thiosulfate, $Na_2S_2O_3$, is a valuable reagent, possessing a variety of uses in pharmacy and industry.

Metallic thiosulfates are commonly prepared by boiling metallic sulfite solutions with sulfur:

$$Na_2SO_3 + S \rightarrow Na_2S_2O_3$$

The sodium thiosulfate thus formed is obtained in crystalline form upon the evaporation of the resulting solution. The starting materials for this method of preparation, on a commercial scale, consist of soda ash, Na_2CO_3, and sulfur dioxide, which react to form the sodium sulfite:

$$Na_2CO_3 + 2SO_2 + H_2O \rightarrow 2NaHSO_3 + CO_2$$

$$2NaHSO_3 + Na_2CO_3 \rightarrow 2Na_2SO_3 + H_2O + CO_2$$

Metallic thiosulfates are fairly unstable. Thus, in the presence of oxygen, especially at elevated temperatures or in the presence of oxidizing agents, sodium thiosulfate may be oxidized to sodium sulfate:

$$Na_2S_2O_3 + \tfrac{1}{2}O_2 \rightarrow Na_2SO_4 + S$$

Sodium thiosulfate is also unstable in the presence of acids because free thiosulfuric acid is liberated; it at once breaks down, with the liberation of water, sulfur dioxide and sulfur:

$$Na_2S_2O_3 + 2HCl \rightarrow 2NaCl + (H_2S_2O_3) \rightarrow H_2O + SO_2 + S$$

This reaction is involved in the U.S.P. Identification Tests for Thiosulfates.[31] Also, because of this instability in the presence of acids, standard solutions of sodium thiosulfate cannot be used for quantitative titrations in the presence of excessive acidity. Even the carbonic acid of the atmosphere is a sufficiently strong acid to bring about the above decomposition, and therefore standard solutions of sodium thiosulfate must be restandardized frequently (p. 145). This reaction is used to advantage in treating

scalp diseases and dermatitis with sodium thiosulfate solution. Due to particle size, it may not be possible to rub dry sulfur into the pores of the skin. However, when sodium thiosulfate is decomposed, colloidal sulfur is formed *in situ.*

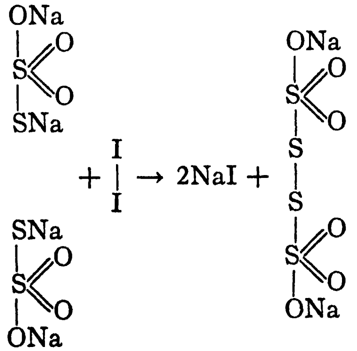
$$Na_2S_2O_3 + H_2CO_3 \rightarrow H_2S_2O_3 + Na_2CO_3$$

$$H_2S_2O_3 \rightarrow H_2SO_3 + S$$

Sodium thiosulfate is a reducing agent and will quantitatively reduce free iodine, being itself oxidized to sodium tetrathionate. This property accounts for the common use of the salt as a reagent in analytical chemistry. In the determination of free iodine in so-called iodometric assays, the color of the free iodine is discharged when it reacts with a standard solution of sodium thiosulfate:

$$2Na_2S_2O_3 + I_2 \rightarrow 2NaI + Na_2S_4O_6$$

Written structurally:



Sodium Tetrathionate

The above reaction occurs in the standardization of Sodium Thiosulfate, Tenth-Normal, U.S.P., when it is standardized against N/10 Iodine Solution.[32] This reaction also occurs in innumerable assays of the U.S.P. and N.F. in which sodium thiosulfate is used for the determination of iodine. The inclusion of a small amount of sodium thiosulfate in the N.F. Potassium Iodide Solution[33] prevents the discoloration of this solution; this discoloration of the solution might be caused by the liberation of free iodine upon the oxidation of the potassium iodide, especially after the solution has been standing for some time.

Other salts of thiosulfuric acid of pharmaceutical interest are calcium thiosulfate, formed in the preparation of Precipitated Sulfur (p. 94) and in the preparation of Sulfurated Lime Solution N.F. (p. 125) and potassium thiosulfate, formed during the preparation of Sulfurated Potassa N.F. (p. 125).

Silver thiosulfate, formed in the "fixing" of a photographic plate by sodium thiosulfate, is also of interest. The solution of sodium thiosulfate, commonly called "hypo," dissolves the unreacted silver bromide from the film, forming soluble sodium bromide and insoluble silver thiosulfate:

$$2AgBr + Na_2S_2O_3 \rightarrow 2NaBr + Ag_2S_2O_3$$

The latter, a white, insoluble compound, is readily soluble in an excess of sodium thiosulfate solution, forming a so-called double salt, soluble in water:

$$Ag_2S_2O_3 + 2Na_2S_2O_3 \rightarrow Na_4Ag_2(S_2O_3)_3$$

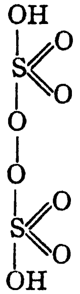
The water-soluble sodium-silver thiosulfate then can be washed out, leaving the unreacted portions of the film transparent.

Sodium thiosulfate used for photographic and other commercial purposes is commonly known as "Sodium Hyposulfite" or simply as "Hypo."[34] This is a chemical misnomer. Sodium hyposulfite is the sodium salt of hyposulfurous acid, $H_2S_2O_4$ (p. 143).

Sodium thiosulfate is little used internally, but it has been recommended as a cathartic and an intestinal antiseptic and in the treatment of iodine, arsenic, bismuth and corrosive sublimate poisoning. It is commonly used externally in solution or lotion in the treatment of fungicidal and parasitic skin diseases, for example, ringworm and taenia infections. Its combination with gold [gold sodium thiosulfate, $AuNa_3(S_2O_3)_2 \cdot 2H_2O$] is used in the treatment of syphilis, rheumatoid arthritis and lupus erythematosis. It must be used with extreme caution, however, because there are many contraindications to its use.

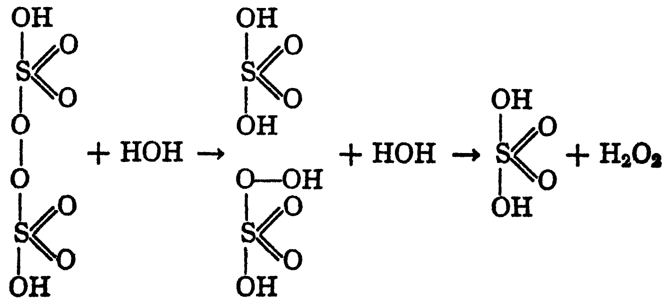
Persulfuric Acid and Persulfates

Another sulfur acid of interest is persulfuric acid, peroxydisulfuric acid, $H_2S_2O_8$, which may be considered to have the structural formula,



The acid, which is unstable and which exists in the free state only in dilute solution, is a strong oxidizing agent, as are its salts. Sulfur peroxide or heptoxide, S_2O_7, is the anhydride corresponding to it. The acid may be prepared by electrolysis of cold, concentrated sulfuric acid; its salts, the persulfates, are prepared commercially by the electrolysis of concentrated solutions of the corresponding metallic acid sulfates. The commonly known salts are ammonium, sodium and potassium persulfates.

This acid and its salts are of pharmaceutical interest because they hydrolyze to form hydrogen peroxide; in fact, this is one of the chief commercial processes for the preparation of concentrated hydrogen peroxide solutions (p. 108). The hydrolysis can be shown to take place in two steps, forming first, peroxymonosulfuric acid (Caro's Acid) and, finally, hydrogen peroxide:



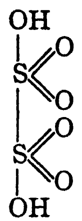
Peroxydisulfuric Acid   Peroxymonosulfuric Acid

In the commercial process the peroxydisulfuric acid is prepared first. Electrolysis of ammonium bisulfate solution forms ammonium persulfate, from which the free acid is liberated and hydrolyzed by sulfuric acid.

The metallic persulfates are commonly used as oxidizing agents in commercial processes. Because of this action, they also have bleaching and deodorizing properties and are used as such. Their strong oxidizing property might be expected from the peroxide oxygen contained in their structure.

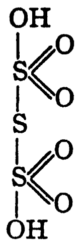
The Thionic Acids

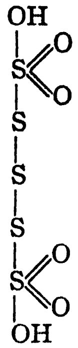
This is an interesting group of acids in which sulfur resembles carbon in its ability to form chainlike compounds in which sulfur is linked to sulfur. There are four commonly known polythionic acids:



Dithionic Acid, $H_2S_2O_6$

Tetrathionic Acid, $H_2S_4O_6$





Trithionic Acid, $H_2S_3O_6$ Pentathionic Acid, $H_2S_5O_6$

Of these polythionic acids, only one, tetrathionic acid, is of pharmaceutical interest, and only because of its relation to thiosulfuric acid. When sodium thiosulfate reacts with iodine, it is oxidized to sodium tetrathionate, $Na_2S_4O_6$, the sodium salt of tetrathionic acid (p. 145). An inspection of its structure reveals the fact that tetrathionic acid is a sulfur analogue of persulfuric acid, $H_2S_2O_8$.

REFERENCES

1. See solubility of Chromium Trioxide, U.S.P. XIII, p. 129.
2. U.S.P. XXII, p. 507; also see Potassium Sulfate.
3. *Ibid.*, p. 835.
4. *Ibid.*, p. 828; also see assay of Exsiccated Sodium Sulfite, p. 508.
5. *Ibid.*, p. 827. Commercial samples of this nature, known also as "Oleum," contain varying amounts of SO_3.
6. U.S.P. XIII, p. 433.
7. U.S.P. XIII, p. 680.
8. See Cottonseed Oil, p. 152, and Estradiol, p. 206, U.S.P. XIII.
9. N.F. VIII, p. 530, and others.
10. U.S.P. XIII, p. 498.
11. N.F. VIII, p. 447, test for identity.
12. U.S.P. XIII, p. 794.
13. *Ibid.*, p. 507.
14. *Ibid.*, p. 845.
15. N.F. VIII, p. 313.
16. U.S.P. XIII, p. 62.
17. N.F. VIII, p. 567.
18. U.S.P. X, p. 154.
19. *Ibid.*, p. 219.
20. U.S.P. XIII, p. 129.
21. *Ibid.*, p. 812.
22. *Ibid.*, p. 663.
23. U.S.P. XIII, p. 597; N.F. VIII, p. 51.
24. U.S.P. XIII, pp. 132, 511; N.F. VIII, p. 122.
25. U.S.P. XIII, p. 304.
26. *Ibid.*, p. 552.
27. *Ibid.*, p. 544.
28. N.F. VIII, p. 519.
29. U.S.P. XIII, p. 663.
30. *Ibid.*, p. 232.
31. *Ibid.*, p. 663; also p. 508.
32. *Ibid.*, p. 866.
33. N.F. VIII, p. 412.
34. U.S.P. XIII, p. 508.

10

Elements of Group V

ELEMENTS—THE NITROGEN SUBGROUP

Of the elements in group V of the periodic table, only those of the nitrogen subgroup, viz., nitrogen, phosphorus, arsenic, antimony and bismuth, are of pharmaceutical importance and only those will be taken up in this chapter.

History. Arsenic and antimony were known to the ancients, probably in the free state as well as in combination. The black sulfide of antimony has been used for ages by oriental women for painting their eyebrows. The Hebrew and Arabic name for this fine black powder is *kohl* which, when coupled with the definite article, *al*, became *alkohl* (meaning literally "the finest"). This was changed to alcohol, from which came the present day use of the term to designate organic alcohols. It is referred to in the work of Pliny as *Stibium*, while in writings ascribed to the physician and alchemist, Geber, and to Basil Valentine (p. 37) it is first called Antimonium. Valentine also described its method of preparation.

The yellow and red sulfides of arsenic, known as orpiment and realgar, respectively, were known and used by the ancients as pigments. Free arsenic was prepared by the alchemists by sublimation, and white arsenic, the trioxide, was also known and used by them.

Bismuth does not appear to have been well known by the ancients and was not used by them as were arsenic and antimony. It was also described in the writings of Valentine.

Phosphorus was prepared in the free state before any of its compounds were recognized, although the name phosphorus had already been given to substances such as barium sulfide which showed phosphorescent properties. The alchemist Brand is generally credited with preparing it in the late 1660's by distilling residues obtained by the evaporation of urine. Gahn, about ten years later, discovered its existence in bones, and about the same time Scheele prepared phosphorus from bone ash.

Nitrogen, like oxygen, long escaped observation because it was a gas. In 1772, Rutherford in Edinburgh observed that air which had been exhausted by animals would support neither combustion nor respiration, and Scheele showed the gas which remained to be a normal constituent of air. Lavoisier proved that the gas was a simple substance and named it *azote* because it did not support life. Chaptal later (1823) named it nitrogen (former of nitre) because of its presence in saltpeter.

Occurrence. Nitrogen in the free state makes up about 80 per cent of the earth's atmosphere. In inorganic combination with oxygen and metals, especially sodium and potassium, it is found in nature as nitrates, sodium nitrate occurring in large deposits as Chile saltpeter. In organic combination, nitrogen is an essential constituent of all plant and animal tissues and is found in proteins, amines, alkaloids and other nitrogenous compounds. The human body contains about 3 per cent nitrogen in combination.

Phosphorus, because of its great affinity for oxygen and other elements, does not occur in the free state in nature but is widely distributed in inorganic combination, especially in phosphates. Calcium phosphate is the chief naturally occurring salt and is a constituent of rocks and soils; it is found in large phosphate rock deposits in the southeastern states, especially Florida, in Tennessee, in the western United States, in North Africa, in Russia and in other places in the earth's surface, where it supposedly has been formed from the remains of prehistoric animals. Phosphorus, like nitrogen, is an essential constituent of all plant and animal tissues. It occurs in both organic and inorganic form in the blood, brain, nerves, muscles, teeth and bones, the latter containing a large percentage of tricalcium orthophosphate.

Arsenic is found most frequently in nature in ores in the form of its oxide and sulfide. It is commonly found in many of the sulfide ores in combination with other metals such as iron. Realgar, As_2S_2, and orpiment, As_2S_3, are two of its most common minerals. Because of the occurrence of sulfides of arsenic with the sulfides of other metals, sulfur and its compounds and metals prepared from these ores are liable to be contaminated with arsenic, thus necessitating the U.S.P. and N.F. tests for arsenic impurity in many of the finished products.

Antimony is found most frequently in nature as the sulfide and oxide. Stibnite, or antimony glance, Sb_2S_3, is its most common sulfide.

Bismuth is a more rare element from the standpoint of occurrence. It occurs both in the free state and in combination in certain minerals as the sulfide and oxide.

Methods of Formation and Preparation.

I. Dissociation of the Hydride.

$$2\cancel{N}H_3 \rightarrow \cancel{N}_2 + 3H_2$$

A. $2NH_3 \xrightarrow{\text{energy}} N_2 + 3H_2$

At ordinary temperatures, ammonia is a stable compound. When heated at a high temperature or when an electric spark is passed through it, ammonia is dissociated into its constituent elements. The reaction, however, is reversible.

B. $2PH_3 \xrightarrow{\text{energy}} 2P + 3H_2$

Phosphine is readily dissociated into its constituent elements by heat.

C. $2AsH_3 \xrightarrow{\text{energy}} 2As + 3H_2$

The above reaction takes place when arsine is heated in the absence of air, as, for example, in carrying out the Marsh test for arsenic, when the outlet tube is heated and a mirrorlike deposit of arsenic is formed on the inside of the tube.

D. $2SbH_3 \xrightarrow{\text{energy}} 2Sb + 3H_2$

If antimony is present in the substance being tested for arsenic by the Marsh test, a deposit of antimony similar to the arsenic mirror will be formed when the outlet tube is heated. These two metals may be differentiated by the fact that arsenic is soluble in a solution of sodium hypochlorite while antimony is insoluble in this reagent.

II. Oxidation of the Hydride.

$$4\cancel{N}H_3 + 3O_2 \rightarrow 2\cancel{N}_2 + 6H_2O$$

A. $4NH_3 + 3O_2 \rightarrow 2N_2 + 6H_2O$

The above reaction is difficult to carry out if oxygen is used as the oxidizing agent. When chlorine, hypochlorite or copper oxide is used, however, the oxidation proceeds readily.

The heating of ammonium nitrite and the oxidation of urea by sodium hypobromite solution (p. 30) are variations of this method. In the former, the nitrous acid produced oxidizes the ammonia to nitrogen, being itself reduced to nitrogen:

$$NH_4NO_2 \xrightarrow{\Delta} [NH_3 + HNO_2] \rightarrow N_2 + 2H_2O$$

B. $4PH_3 + 3O_2 \rightarrow 4P + 6H_2O$

Because of the ease with which phosphorus combines with oxygen, it cannot be produced by the action of oxygen on phosphine. If, however, phosphine is burned with limited access to air, as in a test tube, phosphorus is deposited.

C. $4AsH_3 + 3O_2 \rightarrow 4As + 6H_2O$

In the Marsh test for arsenic, when the mixture of hydrogen and arsine is ignited at the end of the delivery tube and the flame is cooled below the temperature necessary for the formation of oxides of arsenic, by a cold porcelain plate held in the flame, a mirrorlike deposit of free arsenic is formed upon the surface of the plate.

D. $4SbH_3 + 3O_2 \rightarrow 4Sb + 6H_2O$

If antimony is present, a deposit of antimony will be formed along with, or in place of, the arsenic mirror under the same conditions. The two metals may be differentiated on the basis of their solubility in sodium hypochlorite solution.

III. Reduction of the Oxide.

$$\cancel{N}_2O_5 + 5C \rightarrow 2\cancel{N} + 5CO$$

$$\cancel{N}_2O_3 + 3C \rightarrow 2\cancel{N} + 3CO$$

A. $2NO + 2Cu \rightarrow N_2 + 2CuO$

When the oxides of nitrogen are passed over red-hot copper, nitrogen and cupric oxide are formed.

B. $P_2O_5 + 5C \rightarrow 2P + 5CO$

This reaction was involved in the discovery of phosphorus by Brand (p. 148); he distilled urine residues with sand, the carbon being furnished by charring of organic matter in the urine. It is also the final reaction by which phosphorus is obtained on a commercial scale. The chief commercial source of phosphorus is the phosphate rock deposits, in which it is present mainly as tricalcium orthophosphate. This material is treated at a high temperature in an electric furnace with a mixture of silica, in the form of sand, and carbon, in the form of coke. At this high temperature, the silica converts the calcium phosphate into calcium silicate and phosphorus pentoxide:

$$Ca_3(PO_4)_2 + 3SiO_2 \xrightarrow{\Delta} 3CaSiO_3 + P_2O_5$$

The phosphorus pentoxide is reduced by the carbon to free phosphorus (see B), which distills off and is condensed to solid form under cold water.

C. $As_2O_3 + 3C \rightarrow 2As + 3CO$

D. $Sb_2O_3 + 3C \rightarrow 2Sb + 3CO$

E. $Bi_2O_3 + 3C \rightarrow 2Bi + 3CO$

Arsenic, antimony and to some extent, bismuth, are commonly prepared from their oxide ores by reducing them with carbon. When they exist in the ore as sulfides, they may first be converted into the oxide by roasting:

$$2As_2S_3 + 9O_2 \xrightarrow{\Delta} 2As_2O_3 + 6SO_2$$

IV. Reduction of the Sulfide.

$$\cancel{N}_2S_3 + 3Fe \rightarrow 2\cancel{N} + 3FeS$$

A. $As_2S_3 + 3Fe \rightarrow 2As + 3FeS$

B. $Sb_2S_3 + 3Fe \rightarrow 2Sb + 3FeS$

C. $Bi_2S_3 + 3Fe \rightarrow 2Bi + 3FeS$

This method of preparation is applicable to the preparation of those elements which occur in ores as sulfides. Iron is usually employed as the reducing agent, the ferrous sulfide being a significant by-product of the process. Thus, arsenic may be prepared from orpiment, realgar, arsenopyrites, etc.; antimony may be prepared from stibnite and bismuth from bismuth glance.

V. Nitrogen from the Air. In addition to the above-described chemical methods by which nitrogen may be prepared, it is also produced in commercial quantities from the atmosphere. It is produced from the atmosphere by the fractional distillation of liquid air, by passing air over heated copper or by burning phosphorus in air, by which means oxygen is separated from the nitrogen component of air. Details of these

methods can be found in books on industrial chemistry.

Physical Properties. The physical properties of the elements of this group are shown in Table 25. The table serves to show the more or less regular gradation in the properties of the elements and also the differences between them.

TABLE 25. PROPERTIES OF THE ELEMENTS OF THE NITROGEN SUBGROUP

NAME	NITROGEN	PHOSPHORUS	ARSENIC	ANTIMONY	BISMUTH
Atomic weight	14.01	30.98	74.91	121.76	209.00
Physical state	Gas	Solid	Solid	Solid	Solid
Melting point (°C.)	−210	44	814 (36 atm.)	625	270
Boiling point (°C.)	−196	280	Sublimes	1,380	1,470
Color	White (solid)	White	Gray	Silver-white	Reddish-white
Specific gravity	0.967 (air)	1.812	5.7	6.7	9.8

Nitrogen at ordinary temperatures is a colorless, odorless and tasteless gas, very slightly soluble in water. It is one of the more difficult gases to liquefy, its critical temperature being −147° C. and its critical pressure 35.5 atmospheres.

Phosphorus is an allotropic substance, existing in several different solid forms. When freshly prepared, phosphorus is a translucent, yellowish-white substance with a very waxy consistency. This is known as white or yellow phosphorus. At lower temperatures it becomes hard and brittle, breaking with a crystalline fracture. When heated out of contact with air, yellow phosphorus is gradually converted into red phosphorus; at still higher temperatures it changes to the black variety. When phosphorus is exposed to light, the same changes take place, but very slowly. At low temperatures the exposed surface becomes at first opaque, then reddish and occasionally black.[1] Table 26 shows the differences in the properties of the two forms of phosphorus.

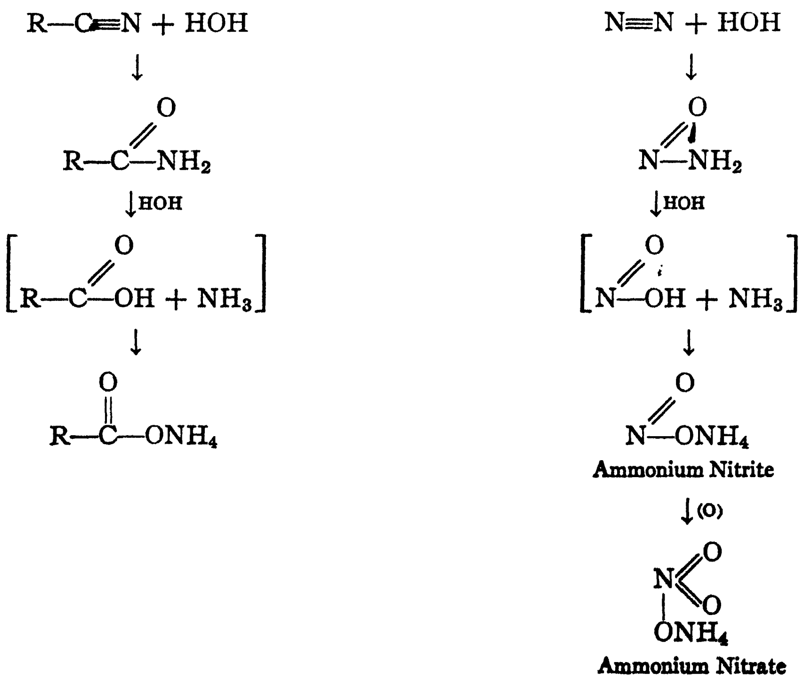
As seen in Table 25, arsenic, antimony and bismuth resemble each other physically in most respects. They all exist as crystalline, metallike substances, the metallic character increasing with increase in atomic weight of the element. Arsenic and antimony, like phosphorus, may occur in several allotropic forms. Bismuth is difficult to pre-

TABLE 26. PROPERTIES OF WHITE AND RED PHOSPHORUS

PROPERTY	WHITE PHOSPHORUS	RED PHOSPHORUS
Odor	Garliclike	Odorless
Melting point (°C.)	44	600 (under pressure)
Specific gravity	1.812	2.10
Solubility	Readily in CS_2, turpentine, olive oil, etc.	Insoluble in these solvents
Ignition temperature (°C.)	30	240
Action with air	Oxidizes with phosphorescence	None
Action with NaOH	Very energetic	None
Action with halogens	Spontaneous	None until heated
Toxicity	Violent poison	Nonpoisonous

pare in the pure state, hence its physical properties are not so well known.

Chemical Properties. Nitrogen is extremely indifferent chemically; it unites with none of the elements at ordinary temperature and with only a few at higher temperatures. Advantage is often taken of this chemical inertness in the estimation of nitrogen-containing compounds, such as the estimation of urea in urine (p. 30), by measuring the amount of nitrogen liberated by oxidation of the compound. Although nitrogen will unite with none of the elements at ordinary temperatures, when an electric spark is passed through moist air, as in thunder storms, both ammonia and oxides of nitrogen are formed. These, upon uniting, form ammonium nitrite and ammonium nitrate, which are carried to the soil by the rain water and are used by plants. In a similar manner, large quantities of nitrites and nitrates are manufactured by the electrolysis of nitrogen of the air. The reactions involved in this hydrolysis of nitrogen may be compared to the hydrolysis of an organic cyanide to form the ammonium salt of the corresponding acid:



Nitrogen in most of its compounds is trivalent toward electropositive elements or groups of elements and either trivalent or pentavalent toward electronegative elements or groups of elements.

Phosphorus, unlike nitrogen, is very active chemically, uniting readily with oxygen, halogens and most other elements. Especially characteristic is its strong affinity for oxygen; upon exposure to the air, phosphorus emits white fumes which are luminous in the dark and have an odor somewhat resembling that of garlic. Upon longer exposure to the air, it ignites spontaneously. The white fumes thus formed are oxides of phosphorus, the luminescence apparently is a transformation of chemical energy into light, and the garliclike odor is due to the formation of ozone. The spontaneous ignition is due to the rapid oxidation of phosphorus as the reaction proceeds and the heat increases. When treated with nitric acid, phosphorus is quickly oxidized to P_2O_5, which dissolves in the reaction mixture, forming phosphoric acid. Because of its great reactivity, phosphorus must be

stored under water and protected from heat, light and the atmosphere.[1]

Phosphorus combines readily with other electronegative elements, such as the halogens and sulfur, and also with some metals. Toward electropositive elements or groups of elements, it exhibits a valence of three and toward electronegative elements or groups of elements it exhibits valences of three and five. In its chemical properties, phosphorus acts as an acidic element, manifesting its nonmetallic nature in its oxides.

Arsenic is on the borderline between the metals and nonmetals and is frequently termed a metaloid. While its physical properties resemble those of the metals, in its chemistry it behaves more frequently as a nonmetal, forming acids rather than bases (p. 186). Arsenic will burn to form the oxide, As_2O_3, when heated in the air and will also combine directly with electronegative elements like the halogens and sulfur, as well as with certain metals. It is oxidized by nitric or sulfuric acid to arsenic acid, H_3AsO_4. In its compounds, arsenic is trivalent toward electropositive elements or groups of elements and either trivalent or pentavalent toward electronegative elements or groups of elements. Its trivalent combinations are generally more stable than are the pentavalent combinations.

Antimony, like arsenic, may behave either as a metal or nonmetal; it is, however, more metallic than arsenic and although its oxides function more frequently as acidic substances, compounds in which they behave as bases are by no means rare. When heated, antimony will burn to the oxide, Sb_2O_3; it also unites directly with the halogens. Like arsenic, it is trivalent toward electropositive elements or groups of elements and either trivalent or pentavalent toward electronegative elements or groups of elements.

Bismuth, which resembles antimony physically, is much more metallic in character and generally behaves as a basic element. Its salts, however, are readily hydrolyzed by water, forming basic salts and liberating free acid, as in the case of the preparation of the basic or subsalts of bismuth of the U.S.P. and the N.F. (p. 183). When heated in the air, bismuth forms the trioxide, Bi_2O_3, and also unites directly with the halogens. Although bismuth will form the pentoxide, Bi_2O_5, and a few other compounds in which it behaves as a pentavalent element, it is usually trivalent in its compounds. Its acid properties are weak, but alkali bismuthites, i.e., salts of bismuthous acid, are known.

In summary, the relationships in chemical properties among the elements of this group may be expressed as follows:

1. In general, the affinity for hydrogen decreases with an increase in the atomic weight of the elements.
2. The affinity for halogens increases with an increase in the atomic weight of the elements.
3. The affinity for oxygen and sulfur decreases with an increase in the atomic weight of the elements, although phosphorus has the greatest affinity for oxygen.
4. The metallic character increases with an increase in the atomic weight of the elements.

Uses. Nitrogen has no medicinal use as such. It is used in industry largely for the production of ammonia, cyanamide, nitric acid and nitrates. It is also used to fill high temperature thermometers and incandescent light bulbs and is used extensively in the laboratory to furnish an inert atmosphere, thus preventing easily oxidizable substances from coming in contact with the air. It is used in some ampules for the same purpose.

Although phosphorus was contained in the N.F. VII in three forms, viz., Phosphorus, Elixir of Phosphorus and Phosphorated Oil, it is not contained in the present edition and is little used as such in modern medicine. Some authorities have claimed that it is of benefit as a general nerve tonic in cases of nervous and sexual exhaustion, and in certain skin diseases. Its use in rickets in the form of phosphorized cod liver oil has also been advocated. The most common industrial use for phosphorus is in the manu-

facture of matches, the red variety being used for this purpose because of its lower toxicity. Large amounts of white phosphorus were used in World Wars I and II in the preparation of tracer and incendiary bullets and incendiary ammunition and bombs and for the production of smoke screens. Small amounts of phosphorus are used in the preparation of rat poison. Compounds of phosphorus are widely used for various purposes.

Arsenic is used most often in the preparation of arsenical drugs, both organic and inorganic. The element itself is insoluble and nontoxic, but its soluble compounds are protoplasmic poisons and are very toxic in sufficiently large doses. In its inorganic compounds, arsenic is used for its tonic and alterative effects. In addition to its medicinal uses, arsenic is widely used for the control and destruction of insects, rodents and other vermin in such compounds as Paris green (p. 190), calcium arsenate, sodium arsenite, lead arsenite, etc. In industry, arsenic is used chiefly in making alloys; in making shot, small amounts of it are added to lead in order to harden the metal and make the shot more nearly spherical.

Arsenic poisoning is not an infrequent occurrence because of the improper safeguarding of arsenical drugs, rat poisons and insecticides. Acute arsenic poisoning is characterized by violent gastro-intestinal irritation; this is followed by vomiting, diarrhea and other characteristic symptoms. First-aid treatment consists of the administration of an emetic to empty the stomach; this is followed by the administration of an arsenic antidote of ferric and magnesium hydroxides (p. 190).

Antimony and bismuth, like arsenic, are used in medicine in the form of their inorganic and organic compounds. The former popularity of antimony preparations has declined greatly, but recent interest has been created in their use in the treatment of protozoan infections. The use of Antimony and Potassium Tartrate (Tartar Emetic) as an emetic has been largely discontinued, but it is still used in small amounts in cough preparations as an expectorant. Bismuth preparations are used in the treatment of syphilis. The insoluble bismuth compounds, such as bismuth subcarbonate, subnitrate and other subsalts, in the form of dusting powders, ointments, powders, etc., are used as protective agents on open wounds and on mucous surfaces. Internally, the basic bismuth salts also exert a mild astringent action in conditions of gastritis, hyperacidity, diarrhea, etc. Poisoning by antimony or bismuth is rare and usually is accidental. In industry, antimony and bismuth are used largely for the preparation of alloys with other metals.

HYDRIDES OF THE ELEMENTS

As noted under their chemical properties (p. 152), the elements of the nitrogen subgroup are trivalent toward electropositive elements; therefore, the more common hydrides of this group may be represented by the general formula, $\text{₦}H_3$, where ₦ stands for the element concerned. The known hydrides of this formula are ammonia, NH_3; phosphine, PH_3; arsine, AsH_3, and stibine, SbH_3. Stable compounds of bismuth with hydrogen are not known.

Other hydrides of some of these elements are also known. The most common of these are hydrazine, N_2H_4; hydrazoic acid, N_3H; liquid phosphine, P_2H_4, and solid phosphine, P_4H_2.

History. Ammonia is by far the most important and most commonly known of the trihydrides. Because of its formation from natural processes, i.e., the decomposition of nitrogenous substances, it has been known for a long time. Sal ammoniac, ammonium chloride, was prepared from camels' dung in the oasis near the temple of Jupiter Ammon in Egypt, whence it derives its name. Glauber, in the middle of the seventeenth century, by distilling sal ammoniac with lime, prepared a liquid which he called

"spiritus volatilis salis ammoniaci." A similar liquid, later prepared by destructive distillation of the hoofs and horns of animals, was called "spirits of hartshorn." Joseph Priestley, in 1774, first prepared ammonia gas by treating sal ammoniac with lime and collecting the gas over mercury. A similar, earlier attempt to prepare ammonia by using his pneumatic trough had failed because ammonia was absorbed by the water. Because of its strong alkaline properties, Priestley called the gas "alkaline air." The composition of ammonia was determined by Berthollet in 1803.

Occurrence. As stated above, ammonia is found among the products resulting from the decomposition of nitrogenous substances, hence it occurs chiefly in the form of salts, in the soil and in natural waters. Ammonia is present in small amounts in the atmosphere, chiefly as ammonium salts which have been formed from the electrolysis of nitrogen (p. 152).

Phosphine, arsine and stibine are less stable than ammonia and do not occur free in nature. Small amounts of phosphines are believed to be produced by the decomposition of organic matter. The light which sometimes appears at night over bogs and marshes, known as "will-o'-the-wisp," is ascribed to the spontaneous ignition of these compounds, which in turn ignite small amounts of methane, causing small intermittent fires.

Methods of Formation and Preparation.

I. DIRECT UNION OF THE ELEMENTS.

A. $N_2 + 3H_2 \overset{\Delta}{\rightleftharpoons} 2NH_3 + 24\ \text{Cal.}$

When a mixture of nitrogen and hydrogen is heated, direct union takes place and small amounts of ammonia are formed, but the reaction is reversible. This reaction is the basis of the Haber Process for the production of synthetic ammonia. This process was developed first in Germany prior to World War I and has since been modified many times. The rate of reaction is considerably accelerated by higher temperatures, but at these higher temperatures the ammonia is dissociated into nitrogen and hydrogen. The original process made use of pressures of 100 to 200 atmospheres and a temperature of 500 to 600° C.; catalysts composed chiefly of iron oxide containing other metals such as cobalt, uranium, molybdenum, etc., were used. More recent modifications vary the operating conditions by using higher pressures, lower temperatures and different catalysts.

B. $2P + 3H_2 \overset{\Delta}{\rightarrow} 2PH_3$

If red phosphorus is heated in an atmosphere of hydrogen, small amounts of the phosphines may be formed, but they are unstable and susceptible to dissociation.

C. $2As + 3H_2 \rightarrow 2AsH_3$

D. $2Sb + 3H_2 \rightarrow 2SbH_3$

When testing for the presence of arsenic by the Marsh test or the Gutzeit test (p. 149), the substance suspected of containing arsenic is placed in a hydrogen generator and reduced by hydrogen. It is quite possible that any arsenic compounds present are first reduced to the element and that the arsenic so formed then combines with hydrogen. Antimony compounds, if present, behave in the same way.

II. REDUCTION OF OXYGEN COMPOUNDS ("-IDES, -ITES, AND -ATES") OF THE ELEMENT.

A. $HNO_3 + 4H_2 \rightarrow 3H_2O + NH_3$

B. $HNO_2 + 3H_2 \rightarrow 2H_2O + NH_3$

Ammonia may be formed by the reduction of nitric acid or nitrous acid, or by the reduction of their salts, but this is not used as a method of preparation.

C. Phosphine, likewise, may be formed by the reduction of oxygen-containing compounds of phosphorus, but this is of little significance as a method of preparation.

D. $As_2O_3 + 6H_2 \rightarrow 3H_2O + 2AsH_3$

E. $Sb_2O_3 + 6H_2 \rightarrow 2H_2O + 2SbH_3$

In the production of arsenic in the Marsh and Gutzeit tests, it is possible that arsenic may be reduced directly to arsine instead of first being reduced to the element, as assumed in I. Either possibility accounts equally well for the formation of the hydride. Antimony, if present, would behave in the same way.

III. ACTION OF ALKALI ON THE ELEMENT. Phosphine is the only hydride of the elements of this group prepared in this way:

A. $4P + 3KOH + 3H_2O \rightarrow 3KH_2PO_2 + PH_3$

B. $8P + 3Ca(OH)_2 + 6H_2O \rightarrow 3Ca(H_2PO_2)_2 + 2PH_3$

In the preparation of metallic hypophosphites by the action of the appropriate metallic hydroxide on phosphorus (p. 194), phosphine is formed as a by-product. The reaction as shown above probably does not show everything that happens since some of the other phosphines are produced at the same time.

IV. ACTION OF WATER (HYDROLYSIS) ON A METALLIC "-IDE" OF THE ELEMENT.

The hydrolysis of metallic nitrides, phosphides, arsenides and stibides forms the gaseous trihydrides of the corresponding element. The alkali "-ides" are usually hydrolyzed by water alone, while the other metallic "-ides" require acid to bring about the hydrolysis:

A. $Mg_3N_2 + 6H_2O \rightarrow 3Mg(OH)_2 + 2NH_3$

B. $RCN + 2H_2O \rightarrow RCOOH + NH_3$

Hydrolysis of organic cyanides, which may be regarded as nitrides of carbon, results in the formation of ammonia. In the same way, the hydrolysis of calcium cyanamide, which may be regarded as a nitride of carbon, is one of the important commercial sources of ammonia:

$$CaCN_2 + 3H_2O \rightarrow CaCO_3 + 2NH_3$$

In the cyanamide process for the production of ammonia, calcium cyanamide is first prepared by the action of nitrogen on calcium carbide at high temperatures, and the calcium cyanamide is then hydrolyzed by steam under pressure. The fact that calcium cyanamide undergoes a similar hydrolysis in the soil makes it valuable as a fertilizer for supplying nitrogen to plants.

C. $Zn_3P_2 + 3H_2SO_4 \rightarrow 3ZnSO_4 + 2PH_3$

D. $Zn_3As_2 + 3H_2SO_4 \rightarrow 3ZnSO_4 + 2AsH_3$

E. $Zn_3Sb_2 + 3H_2SO_4 \rightarrow 3ZnSO_4 + 2SbH_3$

Arsenic, antimony and sometimes phosphorus may be present as impurities in zinc, combined as the corresponding zinc "-ide." Such compounds, if present, will form the corresponding gaseous trihydride when treated with dilute sulfuric acid.

V. HEATING OUT OF CONTACT WITH AIR (DESTRUCTIVE DISTILLATION) OF ORGANIC SUBSTANCES CONTAINING $-NH_2$, $=NH$ AND $\equiv N$ GROUPS.

A. When organic material is subjected to destructive distillation it decomposes with the formation of the hydrides of the constituent elements. Thus, the carbon is partially converted to methane and its homologues, the oxygen to water, the sulfur to hydrogen sulfide and the nitrogen to ammonia. The historical preparation of "spirits of hartshorn" (p. 155) was an example of this process. Ammonia has also been produced, along with other products, by the destructive distillation of the refuse from slaughterhouses, i.e., bones, blood, skin and other tissues.

One of the large commercial sources of ammonia and its salts is the destructive distillation of coal in the production of coke and gas. The coal gas, with which the ammonia is mixed, is passed through water,

which dissolves out the ammonia and its salts giving a solution known as ammoniacal liquor or ammoniacal gas liquor. When this liquor is treated with lime and then is distilled, all of the ammonia is liberated and is usually absorbed in sulfuric acid to form an impure ammonium sulfate. This product makes a very valuable fertilizer, as such, or it may be used as a source of pure ammonia and for the preparation of other ammonium compounds.

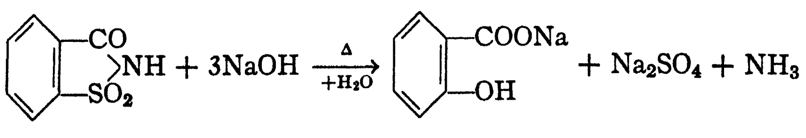
B. Although the addition of an acid or an alkali is unnecessary for the formation of ammonia, such additions often make the method easier and more quantitative. The U.S.P. and N.F. make use of this modified method of making ammonia from organic nitrogenous substances in many tests for identity and in quantitative tests and assays of nitrogen-containing materials. A few of these will be cited as examples.

1. In identification tests for Urethane U.S.P. when the compound is heated with sulfuric acid, ammonium acid sulfate is formed; upon heating with sodium hydroxide solution, free ammonia is formed:[2]

$$\begin{array}{l} \quad NH_2 \\ C{=}O \\ \quad O{-}C_2H_5 \end{array} \quad + H_2SO_4 \xrightarrow[+H_2O]{\Delta} C_2H_5OH + CO_2 + NH_4HSO_4$$

$$\begin{array}{l} \quad NH_2 \\ C{=}O \\ \quad O{-}C_2H_5 \end{array} \quad + 2NaOH \xrightarrow{\Delta} C_2H_5OH + Na_2CO_3 + NH_3$$

2. Saccharin U.S.P., when fused with sodium hydroxide, evolves ammonia:[8]



3. In determining the amount of nitrogen present in organic combination in the alcohol-soluble substances in Beef Extract N.F., the material is heated with concentrated sulfuric acid to break down the organically combined nitrogen to ammonium sulfate. The ammonia then is determined as it is in the Kjeldahl method described below.[4]

4. The decomposition of organic nitrogenous matter by heating it with concentrated sulfuric acid to evolve ammonia forms the basis of the Kjeldahl method for the determination of total nitrogen. This method, the procedure for which is described in detail in the U.S.P. and N.F.,[5] is widely and routinely used for the analysis of many nitrogenous materials, including pure organic compounds, crude drugs, foodstuffs, proteins, fertilizers, etc. There are many modifications of the method; these may be found in standard texts on quantitative analysis. Micro and semimicro Kjeldahl procedures are used routinely in analytical and research laboratories for the determination of nitrogen.

In brief, the nitrogen-containing material is digested in a Kjeldahl flask with a mixture of concentrated sulfuric acid, potassium sulfate and copper sulfate (or other agents to act as catalyst and raise the boiling point of the digestion mixture) until the organic substance is completely decomposed. During this digestion, ammonia is evolved; the ammonia combines with the acid to form ammonium acid sulfate:

$$(CHON)_n(\text{organic compound}) + H_2SO_4 \xrightarrow{\Delta} CO_2 + H_2O + NH_3$$

$$NH_3 + H_2SO_4\ (\text{excess}) \rightarrow NH_4HSO_4$$

The solution then is diluted, an excess of strong sodium hydroxide solution is added cautiously to liberate free ammonia from the salt, granulated zinc is added to prevent bumping, and the solution is distilled through a Kjeldahl connecting bulb into a measured excess of N/10 or N/2 hydrochloric or sulfuric acid. The ammonia, being volatile, is carried over completely into the acid solution where it is fixed as the nonvolatile ammonium salt, while the excess of caustic alkali, being nonvolatile, remains behind in the Kjeldahl flask:

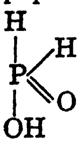
$$NH_4HSO_4 + 2NaOH\ (\text{excess}) \rightarrow Na_2SO_4 + NH_4OH + H_2O$$

$$NH_4OH \xrightarrow{\text{distill}} H_2O + NH_3$$

$$NH_3 + HCl\ (\text{standard solution}) \rightarrow NH_4Cl$$

The excess of the standard acid is determined by titration with standard alkali, and the amount of nitrogen is computed on the basis of the quantity of standard acid to which it is equivalent.

C. Just as substances containing —NH_2, =NH, and ≡N groups yield ammonia upon heating, compounds containing —PH_2, or =PH groups yield phosphine. Thus, hypophosphorous acid, whose structure is

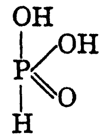


, when heated, yields, for each three moles of the acid, one mole of phosphine and two moles of phosphorous acid:

$$3H_3PO_2 \xrightarrow{\Delta} 2H_3PO_3 + PH_3$$

The salts of hypophosphorous acid behave in the same way, and this reaction is used as one of the identification tests for hypophosphites.[6]

In like manner, phosphorous acid, which in many respects behaves as though its structure is



, decomposes when heated to yield phosphine and phosphoric acid:

$$4H_3PO_3 \xrightarrow{\Delta} 3H_3PO_4 + PH_3$$

VI. Action of Fixed Alkali on an Ammonium or Phosphonium Salt. This is a common method of making ammonia from its salts and is the historical method by which ammonia was prepared from sal ammoniac by the action of slaked lime (p. 155). It is also applicable to the formation of phosphine from phosphonium salts.

A. $NH_4X + NaOH \xrightarrow{\Delta} NaX + H_2O + NH_3$

This reaction is involved in the U.S.P. identification test for ammonium salts and is used repeatedly in tests for the various ammonium salts of the U.S.P. and N.F.[7]

B. In determining the amount of ammonia present in the N.F. Beef Extract, a solution of the extract which may contain ammonia or ammonium salts is heated with barium carbonate; the barium salts of any acids which are present are formed in addition to ammonia, carbon dioxide and water. The ammonia thus liberated is distilled into a measured excess of standard acid and is determined in the usual way.[8]

C. $PH_4X + M'OH \rightarrow M'X + H_2O + PH_3$

Alkalies liberate phosphine from phosphonium compounds even more easily than they liberate ammonia from ammonium salts.

VII. Decomposition of the Ammonium Salt of a Volatile Acid.

A. As a rule, the ammonium salts of volatile acids volatilize without fusing and during this process the salt is decomposed. When the acid formed upon this decomposition is stable at the decomposition temperature, it usually recombines with the

ammonia upon cooling and a sublimate of the original salt is formed. This is the way in which Ammonium Chloride and Ammonium Bromide behave when they are volatilized and the vapors are cooled:

$$NH_4Cl \xrightarrow{\Delta} HCl + NH_3$$
$$NH_3 + HCl \rightarrow NH_4Cl$$

These ammonium salts, therefore, may be sublimed, and this process is used for their purification. However, when boiled, an aqueous solution of either salt will quickly become acid in reaction due to decomposition and the evolution of ammonia.

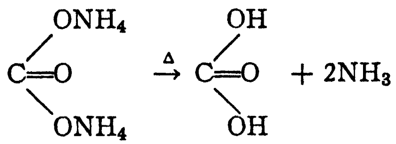
B. With Ammonium Iodide, however, the instability of the hydriodic acid which is formed upon decomposition changes the course of the reaction; when this salt is heated, instead of subliming, it volatilizes and partly decomposes with the evolution of iodine, due perhaps partly to dissociation and partly to the oxidation of the hydrogen iodide formed:

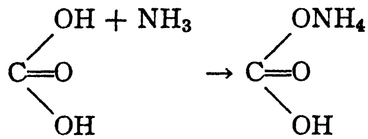
$$NH_4I \xrightarrow{\Delta} HI + NH_3$$
$$2HI \xrightarrow{\Delta} H_2 + I_2$$

or

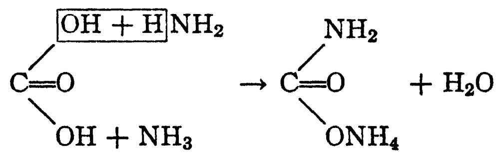
$$2HI + \tfrac{1}{2}O_2 \rightarrow H_2O + I_2$$

C. Ammonium carbonate when heated decomposes into water, carbon dioxide and ammonia; this mixture shows a strongly alkaline reaction. Ammonium Carbonate U.S.P., however, is not the normal salt but a mixture of ammonium acid carbonate, chiefly, plus ammonium carbamate.[9] It is prepared by the sublimation of a mixture of ammonium chloride or ammonium sulfate and calcium carbonate in iron chambers and condensing the vapors; it may be prepared by passing carbon dioxide through ammoniacal gas liquors and purifying the crude product by sublimation. During either of these sublimation procedures the water, carbon dioxide and ammonia recombine in the sublimate to form ammonium acid carbonate and ammonium carbamate in varying proportions:





Ammonium Acid Carbonate



Ammonium Carbamate

Physical Properties. All of the trihydrides are colorless gases which can be condensed to colorless liquids at low temperatures and become solids at still lower temperatures. Table 27 shows the physical properties of the trihydrides of the elements of group V.

All of the trihydrides possess characteristic odors. That of ammonia is quite familiar.

Table 27. Physical Properties of the Trihydrides of the Elements of Group V

Name	Ammonia	Phosphine	Arsine	Stibine
Boiling point (°C.)	−33.5	−86.2	−55	−18
Melting point (°C.)	−78	−132.5	−119	−88
Heat of formation (in Cal./Kg.)	+11.2	+11.6	−36.7	−81.8

Phosphine has an odor resembling that of spoiled fish, while the odor of arsine resembles that of garlic. Ammonia is freely soluble in water, while the other three trihydrides are much less soluble. While ammonia is irritating but not especially toxic when breathed in moderate amounts, phosphine, arsine and stibine are extremely poisonous and have caused the deaths of numerous early investigators engaged in the study of their properties.

Ammonia is readily liquefied at ordinary temperatures by the use of pressure alone. Although liquid ammonia is a poor conductor of electricity, it is an excellent solvent and ionizing medium for other electrolytes. These properties have been utilized to study many reactions, both organic and inorganic, in a liquid ammonia medium. Liquid ammonia also possesses a high latent heat of vaporization (−327.1 Cal./Kg.), absorbing heat from its surroundings during evaporation. Because of this property, it is widely used as a refrigerating agent in the manufacture of ice, in commercial cold storage rooms and in other types of refrigeration. In refrigeration, the ammonia gas is liquefied by compression with a pump; the liquid ammonia then is passed through coils dipping into a salt brine or calcium chloride solution and the pressure is released. The rapid evaporation of the liquid ammonia cools the brine down to low temperatures, and the ammonia gas is led back into the compression chamber, making the process continuous.

Hydrazine, or diamine, $H_2N—NH_2$, is a colorless liquid boiling at 113.5° C. and melting at 1.8° C. It is miscible with water in all proportions and forms a hydrate with water. Hydrazoic acid, N_3H, also known as triazoic acid and azoimide, is a colorless liquid with a disagreeable, penetrating odor. It boils at 37° C. and melts at −80° C.; it is miscible with water in all proportions.

Liquid phosphine, P_2H_4, is a colorless, water-insoluble liquid, boiling at 52° C. and melting at −99° C.; solid phosphine, P_4H_2, is a yellow, odorless, tasteless, water-insoluble powder.

Chemical Properties. The hydrides of the elements of group V, with the exception of those of nitrogen, are very unstable and decompose readily upon heating. They also burn readily; some of the phosphines ignite spontaneously in the air, while a mixture of phosphine and oxygen is explosive. Arsine and stibine decompose spontaneously at room temperature. Ammonia is stable at moderately high temperatures but decomposes into nitrogen and hydrogen at higher temperatures or in the presence of an electric spark (p. 149). Ammonia burns to nitrogen and water in pure oxygen and also is easily oxidized by cupric oxide and chlorine (p. 149).

The properties of the hydrides of nitrogen vary with their composition and structure. Ammonia, NH_3, is a basic substance, forming salts with acids. When ammonia comes into contact with even a very weak acid, it adds on the acid to form a salt:

$$NH_3 + \text{H Acid} \rightarrow NH_4\ \text{Acid}$$

Toward water, ammonia behaves in the same way to form ammonium hydroxide:

$$NH_3 + HOH \rightarrow NH_4OH$$

Ammonium hydroxide is a base and forms salts with acids, by the elimination of water, just as metallic hydroxides form salts:

$$NH_4OH + \text{H Acid} \rightarrow H_2O + NH_4\ \text{Acid}$$

Thus, in the hydroxide and in its salts, the ammonium radical, NH_4^+, behaves like a univalent metallic element, such as sodium or potassium; it will be considered in more detail with those metals (p. 250).

Phosphine, PH_3, resembles ammonia in structure and to some extent in its properties. It is much less basic than ammonia, but it will form salts by the addition of hydrogen halides and sulfuric acid in the same way:

$$PH_3 + HX \rightarrow PH_4X$$

These phosphonium salts, however, are unstable and easily decomposed. Phosphine does not combine with water like ammonia does. Arsine and stibine have no basic properties similar to those of ammonia.

Since the trihydrides other than ammonia give up their hydrogen so easily, they behave as reducing agents. They will reduce not only the usual oxidizing agents, but also will reduce the salts of the heavy metals to the free metal. The reduction of silver nitrate is the most characteristic reaction and forms the basis of the Gutzeit test for detecting small amounts of arsenic as an impurity and in toxicologic examinations. In this test, arsine is produced as it is in the Marsh test (p. 155), by the reduction of the arsenic compound with hydrogen. The arsine is allowed to come into contact with a piece of filter paper moistened with silver nitrate solution. A yellow stain on the paper is a positive test for arsenic; upon standing, the stain changes into black, metallic silver:

$$AsH_3 + 6AgNO_3 + 3H_2O \rightarrow 6HNO_3 + H_3AsO_3 + \underline{6Ag}$$

If antimony is present, the same black stain will be produced but the yellow stain will not appear. The history of both the Marsh and Gutzeit tests has recently been summarized.[10]

Mercury salts are also reduced by arsine. The reduction of mercuric bromide forms the basis of the modified Gutzeit test contained in the U.S.P.;[11] the stain produced on mercuric bromide test paper varies in color and intensity with the amount of arsenic present in the sample. It is believed that, depending upon the amount of arsenic present, complex double compounds of arsine and mercuric bromide are produced as intermediates, accounting for the various colors produced on the test paper. The U.S.P. places an arsenic limit on the sample tested in this manner, and the stain produced is compared with that obtained from a standard arsenic sample.

Ammonia has the property of forming, not only addition compounds, but also substitution compounds; in the latter, one or more of its hydrogens are replaced by another element or group of elements. Compounds of this sort in which one, two and three hydrogens have been replaced by metals are known as amides, imides and nitrides, respectively. Such compounds are formed when the metal is heated with ammonia:

$$2Na + 2NH_3 \rightarrow H_2 + \underset{\text{Sodium Amide or Sodamide}}{2NaNH_2}$$

$$2Ag + NH_3 \rightarrow H_2 + \underset{\text{Silver Imide}}{Ag_2NH}$$

$$3Mg + 2NH_3 \rightarrow 3H_2 + \underset{\text{Magnesium Nitride}}{Mg_3N_2}$$

These compounds are not too stable and are hydrolyzed by water to ammonia and the metallic hydroxide.

Compounds in which one or more of the hydrogens of ammonia have been replaced by an alkyl or aryl group are known as amines; they are commonly classified as primary, secondary or tertiary amines according to the number of hydrogens substituted. However, this classification is open to criticism when viewed in the light of the original conception of the term amine, according to the "theory of types," and when compared with the classification of the organic alcohols. The organic amines, which are considered in detail in the courses in organic chemistry, resemble ammonia in their basic properties.

Compounds in which one of the hydrogens of ammonia has been replaced by an acyl radical are known as acid amides; although there are many examples of inorganic acid amides, the more common ones are derivatives of organic acids and are considered in detail in organic chemistry. Carbamic acid is a compound of this type; in this com-

pound one hydrogen of ammonia is replaced by the carbonic acid radical. Ammonium carbamate (p. 159) and ethyl carbamate are the ammonium salt and ethyl ester, respectively, of this acid, while urea, carbamide, is the diamide of carbonic acid. Many of the natural and synthetic alkaloids and other synthetic medicinal agents containing nitrogen may be regarded as substituted ammonias, e.g., acetanilid, acetophenetidin, etc. These and other alkyl, aryl and acyl substituted ammonias are not within the scope of inorganic pharmaceutical chemistry.

Of the other hydrides of nitrogen, hydrazine or diamine, $H_2N{-}NH_2$, which may be regarded as an amino substitution product of ammonia, is also basic in its properties. Like ammonia, it forms salts with acids by addition and, since it contains two basic nitrogens, can add on not only one but two moles of acid to form either a mono- or disalt, e.g., hydrazine hydrochloride and hydrazine dihydrochloride. Like ammonia, hydrazine can also form substitution products in which one or more of its hydrogens have been replaced by an alkyl or aryl radical and also those in which a hydrogen has been replaced by an acyl radical. These compounds are known, respectively, as substituted hydrazines and hydrazides, analogous to amines and amides. A common example of the former is the U.S.P. reagent Phenylhydrazine, also included in the N.F. as its hydrochloride. Phenylhydrazine is commonly used in organic chemistry as a qualitative reagent for the detection and identification of aldehydes and ketones; it forms a crystalline, sharp-melting phenylhydrazone with the aldehyde or ketone in question:

$$\mathrm{R{-}}\overset{\text{H(or R}')}{\overset{|}{\mathrm{C}}}\mathrm{{=}O + H_2N{-}NH{-}C_6H_5 \rightarrow H_2O + R{-}}\overset{\text{H(or R}')}{\overset{|}{\mathrm{C}}}\mathrm{{=}N{-}NH{-}C_6H_5}$$

Phenylhydrazine may also be used in the quantitative estimation of aldehydes and ketones; an example of this is found in the assay of benzaldehyde according to the N.F. VI procedure.[12] Another application of the quantitative use of a phenylhydrazine is found in the gravimetric determination of camphor in the N.F. VIII Camphor Spirit by weighing the amount of the 2,4-dinitrophenylhydrazone obtained by reacting a measured amount of the sample with 2,4-dinitrophenylhydrazine T.S.[13]

Phenylhydrazine hydrochloride is frequently used as a qualitative reagent in place of free phenylhydrazine because the hydrochloride is more stable and can be kept longer without decomposition. In this case, sodium acetate is usually added to the reaction mixture in order to liberate the free base from its hydrochloride, as in the N.F. Osazone Test Reagent.[14]

A well-known example of an acyl-substituted hydrazine is semicarbazide, carbamic acid hydrazide, $H_2N{-}NH{-}CO{-}NH_2$, which may be regarded as hydrazine in which one hydrogen has been replaced by the carbamic acid radical. Semicarbazide is basic, like ammonia and hydrazine, although less so; it forms salts by the addition of acids, as for example, Semicarbazide Hydrochloride, contained in the U.S.P. as a reagent. Like phenylhydrazine, semicarbazide is also used as a qualitative reagent for the detection and identification of aldehydes and ketones, with which it forms crystalline, sharp-melting semicarbazones:

$$\mathrm{R{-}}\overset{\text{H(or R}')}{\overset{|}{\mathrm{C}}}\mathrm{{=}O + H_2N{-}NH{-}CO{-}NH_2 \rightarrow H_2O + R{-}}\overset{\text{H(or R}')}{\overset{|}{\mathrm{C}}}\mathrm{{=}N{-}NH{-}CO{-}NH_2}$$

Another important derivative of ammonia is hydroxylamine, $H_2N{-}OH$, which may be considered as ammonia in which one hydrogen has been replaced by an OH group. It

has basic properties and, like ammonia, forms salts with acids by addition, e.g., hydroxylamine hydrochloride. It is, however, a much weaker base than either ammonia or hydrazine. It is included as its hydrochloride in the U.S.P. Reagents as well as in Test Solution. Like hydrazine and phenylhydrazine, hydroxylamine is also used as a qualitative reagent for the detection and identification of aldehydes and ketones and may also be used for their quantitative estimation. With aldehydes and ketones it forms crystalline, sharp-melting aldoximes and ketoximes:

$$R{-}\overset{\text{H(or R}')}{\overset{|}{C}}{=}O + H_2N{-}OH \rightarrow H_2O + R{-}\overset{\text{H(or R}')}{\overset{|}{C}}{=}N{-}OH$$

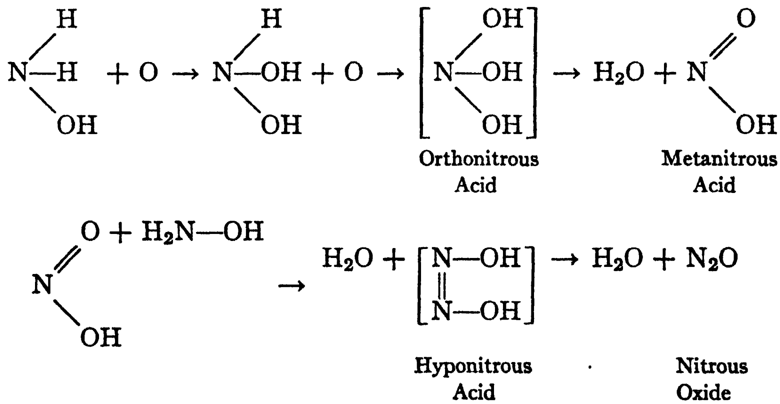
When the hydrochloride is used in place of the free hydroxylamine, sodium or potassium hydroxide is usually added to the reaction mixture to liberate the free base, as in the U.S.P. test solution.[15]

An example of the quantitative application of the above reaction is the assay of N.F. Bitter Almond Oil for its benzaldehyde content.[16]

Both hydrazine and hydroxylamine are active reducing agents, and they are oxidized readily. The fact that hydroxylamine is quantitatively oxidized to nitrous oxide by ferric iron is the basis of its assay by the U.S.P. procedure:

$$2H_2N{-}OH + O_2 \rightarrow N_2O + 3H_2O$$

This reaction *may be considered* to take place in steps, and it is more easily understood this way:



In the U.S.P. assay,[17] a weighed sample of hydroxylamine hydrochloride is treated with an excess of ferric ammonium sulfate in sulfuric acid solution and the reaction is allowed to proceed until all of the hydroxylamine in the sample is oxidized, as shown above, by the ferric iron. The ferric iron is reduced to ferrous iron. The mixture is titrated with N/10 $KMnO_4$, which quantitatively oxidizes the ferrous iron back to the ferric state. The amount of hydroxylamine hydrochloride in the sample is computed in terms of the amount of N/10 $KMnO_4$ to which it is equivalent:

After this reaction has taken place the ferrous iron is oxidized back to the ferric state by the N/10 $KMnO_4$ (p. 96).

Of the other known hydrides of nitrogen, only one, hydrazoic acid, N_3H, will be mentioned. Whereas ammonia is basic in character, hydrazoic acid is acidic, the hydrogen being replaceable by metals to form salts known as metallic hydrazoates or azides. Hydrazoic acid and its salts are highly explosive, lead azide, $Pb(N_3)_2$, being used as a detonator in explosives. Although neither hydrazoic acid nor its derivatives appear to be of pharmaceutical importance, it illus-

$$2NH_2OH + 4FeNH_4(SO_4)_2 \rightarrow H_2O + 2H_2SO_4 + N_2O + 2FeSO_4 + 2Fe(NH_4)_2(SO_4)_2$$

strates a principle which is evident many times in pharmaceutical chemistry, namely, that the basic or acidic character of a nitrogen-containing compound depends upon the nature of the elements or groups surrounding the nitrogen. If these elements or groups are predominantly electropositive, the compound is basic in character; if these elements or groups are predominantly electronegative, the compound is acidic in character. Thus, in ammonia three electropositive hydrogens surround the nitrogen, making the molecule electropositive or basic in character; while in hydrazoic acid, the conditions are reversed, three nitrogen atoms combined with one hydrogen, making the molecule electronegative or acidic in character. The same principle may be illustrated in comparing the properties of aniline and acetanilid; it also explains the acidic character of such compounds as saccharin, the barbiturates, the purine bases and certain alkaloids, and at the same time explains the basic character of the amines and other alkaloids that act like ammonia toward acids.

Uses. The chief industrial uses of ammonia, most of which have been mentioned already, are in the production of ammonium salts, fertilizer, nitric acid and as a raw material in the Solvay process (p. 217). In addition, large quantities are used in refrigeration, as solvents, as an ionizing medium and as a cleansing and water softening agent in ordinary household ammonia.

Table 28 summarizes the forms in which ammonia is contained in the U.S.P. and the N.F.

Medicinally, ammonia is used as a stimulant, as an irritant and as a carminative agent. The inhalation of ammonia from Ammonia Water, the Aromatic Spirit or Ammonium Carbonate, and also oral administration, stimulates the respiratory and vasomotor centers, causing deeper respiration and increased heart action. Since this action is usually a transient one, ammonia is a valuable emergency stimulant in cases of fainting or collapse. Smelling salts usually contain ammonium carbonate as the source of ammonia. The inhalation of too high a concentration of ammonia causes severe irritation. Since it has a rubefacient action, ammonia is commonly used externally in the form of the liniment as a local irritant and counterirritant. In this case also, too high a concentration will cause blistering. Aromatic Spirit of Ammonia is also administered internally as an antacid and carminative, and Ammonium Carbonate, because of its expectorant action, is a common ingredient of cough mixtures. Concentrated ammonia so-

TABLE 28. U.S.P. AND N.F. PREPARATIONS OF AMMONIA

Name	Common Name	Type of Preparation	Strength (Per Cent)
Ammonia Water Stronger, Reagent, U.S.P.	Ammonium Hydroxide	Aqueous	27.0
Strong Ammonia Solution U.S.P.	Stronger Ammonia Water	Aqueous	28.0
Diluted Ammonia Solution U.S.P.	Ammonia Water	Aqueous	9.5
Aromatic Ammonia Spirit U.S.P.	....	Hydro-alcoholic	2 per cent NH_3 plus 4 per cent $(NH_4)_2CO_3$
Ammonia Test Solution U.S.P.	....	Aqueous	10.0
Ammonia Test Solution, Alcoholic, U.S.P.	....	Alcoholic	10.0
Ammonia Liniment N.F.	Hartshorn Liniment	Oily	2.5
Anisated Ammonia Spirit N.F.	....	Hydro-alcoholic	2.0

lutions have much the same destructive effect on the mucous membranes as the caustic alkalies, and the first aid treatment for such cases is the same (p. 254).

The other hydrides of nitrogen, as well as phosphine, arsine and stibine, have no medicinal use.

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2. U.S.P. XIII, p. 596.
3. *Ibid.*, p. 459.
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6. U.S.P. XIII, p. 661.
7. *Ibid.*, p. 658.
8. N.F. VIII, p. 71.
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10. Webster, S. H.: J. Chem. Ed. **24**:487, 1947.
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12. N.F. VI, p. 58.
13. N.F. VIII, p. 115.
14. *Ibid.*, p. 603.
15. U.S.P. XIII, p. 838.
16. N.F. VIII, p. 30.
17. U.S.P. XIII, p. 773.

11

Hydroxides (Oxyacids) of Group V and Their Salts of Pharmaceutical Importance

As noted under their chemical properties (p. 152), the elements of group V exhibit toward electronegative elements or groups of elements valences of five and three. If these valences are satisfied by the electronegative hydroxyl (—OH) group, we may have pentahydroxides and trihydroxides of these elements. These or their partial dehydration products form the oxyacids of the elements of group V. On the following pages a summary of all of these compounds will be given in condensed table form.

PENTAHYDROXIDES

The Acids

With Ꞥ as the general symbol for the elements of group V acting in their pentavalent state, the following pentahydroxides and their partial and complete dehydration products, together with the names, are indicated on the following page.

Of the compounds listed in this table, the pentahydroxides are unstable and little is known concerning them. The monoxide-trihydroxides, the commonly known ortho-ic acids, are, in the case of phosphorus and arsenic, well-known both as such and in the form of their salts. The dioxide-monohydroxides, the commonly known meta-ic acids, of nitrogen, phosphorus and arsenic are also well-known as such and in the form of their salts. Of the pentoxides, that of phosphorus is best known.

Occurrence. Like most acids, those of the elements of group V in their pentavalent state usually occur in nature in the combined state in the form of their salts. Nitric acid and its salts, the nitrates, occur in small amounts in the air and in the soil, formed (as shown on p. 152) by electrolysis of nitrogen during electrical storms. Another source of nitrates in the soil is the action of nitrifying bacteria which live in a symbiotic relationship in the nodules on the roots of leguminous plants. These bacteria have the ability to take nitrogen from the air as it circulates through the soil and convert it into nitrates. The nitrate then can be utilized by the plant and also, in part, remain fixed in the soil. Large deposits of sodium nitrate

$N(OH)_5$ Pentahydroxide	$NO(OH)_3$ Monoxide-trihydroxide (Ortho-ic Acid)	NO_2OH Dioxide-monohydroxide (Meta-ic Acid)	N_2O_5 Pentoxide (-ic Acid Anhydride)
$N(OH)_5$	$NO(OH)_3$ Orthonitric acid	NO_2OH * Metanitric acid	N_2O_5 Nitrogen pentoxide (Nitric acid anhydride)
$P(OH)_5$	$PO(OH)_3$ * Orthophosphoric acid	PO_2OH Metaphosphoric acid	P_2O_5 * Phosphorous pentoxide (Phosphoric acid anhydride)
$As(OH)_5$	$AsO(OH)_3$ * Ortho-arsenic acid	AsO_2OH Meta-arsenic acid	As_2O_5 * Arsenic pentoxide (Arsenic acid anhydride)
$Sb(OH)_5$	$SbO(OH)_3$ Ortho-antimonic acid	SbO_2OH Meta-antimonic acid	Sb_2O_5 Antimony pentoxide (Antimonic acid anhydride)
$Bi(OH)_5$	$BiO(OH)_3$ Orthobismuthic acid	BiO_2OH Metabismuthic acid	Bi_2O_5 Bismuth pentoxide (Bismuthic acid anhydride)

* Compounds that are of pharmaceutical importance and are represented in the U.S.P. or N.F., either as such or in the form of their salts.

occur naturally in certain arid regions. The largest is in Chile; from here much of the sodium nitrate of commerce, as well as iodine (p. 22), is obtained. Supposedly, nitrate is formed in the high regions of the Andes where electrical storms are frequent, and the waters, carrying the dissolved material on their way to the sea, evaporate and deposit the solid sodium nitrate in the arid region. Smaller deposits are found in the western and southwestern regions of the United States.

Orthophosphoric acid, as mentioned (p. 149), occurs as its salts as well as in organic combination in both plants and animals. All fertile soils contain varying amounts of calcium phosphate, and the large rock phosphate beds throughout the world are the important commercial source of phosphorus and its compounds as well as being of prime importance as a source of fertilizer. Combined with glycerol, fatty acids and amino alcohols, phosphoric acid occurs in the biologically important phosphatides or phospholipids, such as lecithins, cephalins, etc., found especially in brain and nerve tissue of animals as well as in plants.

The oxyacids of arsenic, antimony and bismuth in their pentavalent state are relatively unstable and do not occur in nature.

Methods of Formation and Preparation.

I. Hydration of the Oxide.

$$N_2O_5 + H_2O \rightarrow 2NO_2 \cdot OH$$

or

$$N_2O_5 + 3H_2O \rightarrow 2NO(OH)_3$$

Hydration of the pentoxides of the elements of group V will form either the meta-ic acid or the ortho-ic acid, depending upon the extent of the reaction.

A. $N_2O_5 + H_2O \rightarrow 2HNO_3$

Hydration of nitrogen pentoxide will yield metanitric acid, but this is not a method of preparation since nitrogen pentoxide is not common. Nitric acid may be produced, however, by any method by which nitric oxide, NO, is made, provided water and oxygen are present, since the nitrogen dioxide formed by oxidation of the nitric oxide yields nitric acid upon hydration:

$$3NO_2 + H_2O \rightarrow 2HNO_3 + NO$$

Thus, any method for the preparation of nitric oxide or nitrogen dioxide is also a method of preparation of nitric acid; these will be referred to under the oxides of nitrogen (p. 191).

B. $P_2O_5 + H_2O \rightarrow 2HPO_3$

$P_2O_5 + 3H_2O \rightarrow 2H_3PO_4$

Phosphorus pentoxide has a great affinity for water and these reactions take place when it is used as a dehydrating agent in desiccators and in the chemical laboratory. The thick, sticky mass remaining in a desiccator in which P_2O_5 has been used consists chiefly of the metaphosphoric acid. These reactions also form the basis of the commercial manufacture of pure orthophosphoric acid, the phosphorus pentoxide being obtained from pure distilled phosphorus by the action of oxygen. A third example is found in the testing of phosphorus for arsenic or sulfur impurity, as in the N.F. VII,[1] where phosphorus is oxidized by nitric acid to P_2O_5, which then dissolves in water with the formation of orthophosphoric acid.

C. $As_2O_5 + H_2O \rightarrow 2HAsO_3$

$As_2O_5 + 3H_2O \rightarrow 2H_3AsO_4$

If arsenic is present as an impurity in the phosphorus,[1] it is oxidized by the nitric acid to As_2O_5, which then is hydrated by water to ortho-arsenic acid.

II. Action of Acid upon a Suitable Salt.

A. 1. $KNO_3 + HCl \rightarrow KCl + HNO_3$

This reaction is used in the assay of N.F. Potassium Nitrate.[2] The nitric acid thus liberated, being volatile, is driven off, along with the excess hydrochloric acid, by heating on the water bath; the quantity of potassium chloride remaining is determined according to the usual method for determination of chlorides.

2. $NaNO_3 + H_2SO_4 \rightarrow NaHSO_4 + HNO_3$

In former years, the chief commercial source of nitric acid was from Chile saltpeter by means of this reaction. The reaction proceeds because of the greater volatility of the nitric acid produced and is carried out under reduced pressure to prevent undue decomposition. A second molecule of nitric acid cannot feasibly be obtained by action of another molecule of sodium nitrate with the sodium acid sulfate because, at the temperature required for the reaction to take place, too much of the nitric acid would be decomposed.

B. $Ca_3(PO_4)_2 + 3H_2SO_4 \rightarrow 3CaSO_4 + 2H_3PO_4$

This reaction is the basis of one of the commercial methods of preparation of an impure grade of orthophosphoric acid by the treatment of rock phosphate with concentrated sulfuric acid. The acid thus produced is not as pure as that obtained by hydration of phosphorus pentoxide since it contains varying amounts of soluble calcium acid phosphate, $Ca(H_2PO_4)_2$.

C. $Na_2HAsO_4 + 2HCl \rightarrow 2NaCl + H_3AsO_4$

In the assay of N.F. Exsiccated Sodium Arsenate and Sodium Arsenate Solution, the ortho-arsenic acid, liberated in the above manner, is determined by an iodometric titration (p. 27).

III. Oxidation of the Corresponding Acid Less Rich in Oxygen, the "-ous" Acid or "Hypo-ous" Acid.

A. $2HNO_2 + O_2 \rightarrow 2HNO_3$

Since nitrous acid is not stable in the free state for any length of time, the best illustration of this reaction is in the assay of its salts, such as U.S.P. Sodium Nitrite, by oxidation with N/10 $KMnO_4$, which has already been discussed (p. 97).

B. $2H_3AsO_3 + O_2 \rightarrow 2H_3AsO_4$

In the assay of trivalent arsenic compounds of the U.S.P. and N.F. by iodimetric

titration, previously described (p. 40), arsenous acid is oxidized by N/10 Iodine to arsenic acid.

C. $2H_3SbO_3 + O_2 \rightarrow 2H_3SbO_4$

This reaction, which is analogous to the oxidation of arsenous acid to arsenic acid, takes place in the iodimetric assay of trivalent antimony compounds, such as U.S.P. Antimony Potassium Tartrate. It should be noted that this assay, as well as that of trivalent arsenic compounds, is carried out in the presence of an excess of sodium bicarbonate, sufficient not only to form the salts of the acids but also to neutralize the hydriodic acid formed; if sodium bicarbonate were not present, the reaction would be reversible, with the hydriodic acid reducing the "-ic" acid back to the "-ous" state (p. 27).

D. $2H_3PO_2 + O_2 \rightarrow 2H_3PO_3 \xrightarrow{+O_2} 2H_3PO_4$

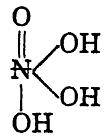
In the U.S.P. Diluted Hydriodic Acid, a limited amount of hypophosphorous acid is allowed as a reducing agent to prevent the formation of free iodine by atmospheric oxidation of the hydrogen iodide (p. 26). Here the hypophosphorous acid acts like arsenous acid and antimonous acid in B and C above; any free iodine which may be formed by oxidation of the hydrogen iodide is immediately reduced back to hydrogen iodide, the hypophosphorous acid being oxidized at the same time to phosphorous acid and finally to phosphoric acid. In the N.F. Ferrous Iodide Syrup (p. 68), even though sugar is a reducing agent it is not active enough to protect ferrous iodide against oxidation, so hypophosphorous acid is included for added protection. By the same mechanism, ammonium hypophosphite, the presence of one per cent of which is permitted in the N.F. Ammonium Iodide as a stabilizing agent, prevents the oxidation of that product.[8]

Another illustration of this reaction is furnished in the assay of the salts of hypophosphorous acid, the hypophosphites, by quantitative oxidation with N/10 bromine solution. These will be considered in more detail under hypophosphorous acid (p. 195).

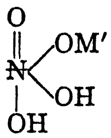
Properties. As mentioned before, the pentahydroxides of this group, because of their instability, are not commonly known. The first dehydration product, the ortho-ic acid, is more stable. Orthonitric acid, however, is unstable and is rarely encountered even in its salts. Ortho-antimonic acid does not exist very long in the free state but readily decomposes into its anhydride and water; salts of antimonic acid, most commonly the meta-antimonates, are known. Bismuthic acid is even less stable and salts of the acid, while known, are probably not pure compounds. Orthophosphoric acid is most commonly known as a heavy, syrupy liquid from which it is possible to obtain the colorless acid in crystalline form. It is miscible with water in all proportions. Ortho-arsenic acid is a white, crystalline, water-soluble compound.

The acidic character of the acids of this group decreases with an increase in the atomic weight of the element, from nitrogen to bismuth, with a corresponding increase in basic character. Arsenic, antimonic and bismuthic acids provide good illustrations of amphoteric (amphiprotic) compounds, i.e., they may act either as acids or bases. This property is even more clearly illustrated by the corresponding "-ous" acids of these elements (p. 186).

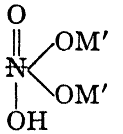
The ortho-ic acids having three acidic hydrogens, form three types of salts, depending on whether one, two or all three of the hydrogens are replaced by metal. Much confusion results from the different names given these salts, as is evident from the names by which some of the U.S.P. and N.F. examples are known (p. 176). For the sake of avoiding confusion, the following systematic method of nomenclature may be followed to advantage:



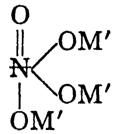
Ortho-ic Acid



Monometal Dihydrogen Ortho-ate

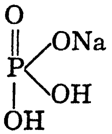


Dimetal Monohydrogen Ortho-ate

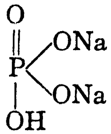


Trimetal Ortho-ate

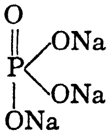
This may be illustrated with the sodium salts of orthophosphoric acid:



Monosodium Dihydrogen Orthophosphate



Disodium Monohydrogen Orthophosphate



Trisodium Orthophosphate

The particular salt formed when the ortho-ic acid is treated with alkali depends upon the amount of the latter added or upon the point at which the reaction is stopped. Thus, when sodium hydroxide is added to orthophosphoric acid in the ratio of one mole of alkali to one of the acid, monosodium dihydrogen orthophosphate is formed by replacing one hydrogen of the acid. The end of this reaction may be indicated by the use of methyl orange, the salt formed being neutral to that indicator:

$$H_3PO_4 + NaOH \rightarrow NaH_2PO_4 + H_2O$$

When sodium hydroxide is added to orthophosphoric acid in the ratio of two moles of alkali to one of the acid, disodium monohydrogen orthophosphate is formed by replacing two hydrogens of the acid. This salt is neutral to phenolphthalein, hence the end of this reaction may be seen by use of that indicator:

$$H_3PO_4 + 2NaOH \rightarrow Na_2HPO_4 + 2H_2O$$

When sodium hydroxide is added to orthophosphoric acid in the ratio of three moles of alkali to one of the acid or when an excess of alkali is added, the trisodium orthophosphate is formed by replacing all three hydrogens of the acid:

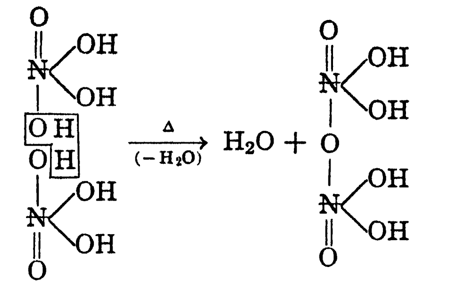
$$H_3PO_4 + 3NaOH \rightarrow Na_3PO_4 + 3H_2O$$

It is therefore necessary in titrating phosphoric acid with a standard sodium or potassium hydroxide solution to specify the indicator to be used in order to know how many hydrogens of the acid are being neutralized. Examples of this are found in the volumetric factors (mille-equivalents) for phosphoric acid and for sodium biphosphate listed under the U.S.P. Sodium Hydroxide, Normal,[4] and in the assays of N.F. Phosphoric Acid[5] and U.S.P. Sodium Biphosphate[6] by titration with this reagent. In the assay of the former, a weighed sample is titrated with normal sodium hydroxide to a phenolphthalein end-point, i.e., two moles of alkali react to form the disodium monohydrogen orthophosphate. In the assay of Sodium Biphosphate, a weighed sample is titrated with normal sodium hydroxide to a phenolphthalein end point, i.e., one mole of alkali converts the monosodium salt into the disodium salt:

$$NaH_2PO_4 + NaOH \rightarrow Na_2HPO_4 + H_2O$$

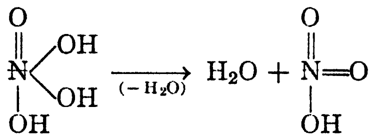
Another example is furnished in the preparation of U.S.P. Sodium Phosphate, Na_2HPO_4 (p. 176), by adding sodium carbonate to orthophosphoric acid until it is neutral to phenolphthalein or until effervescence ceases. No matter how much sodium carbonate is added, only two hydrogens of the acid can be replaced since the disodium monohydrogen orthophosphate formed is as basic as the sodium carbonate.

The ortho-ic acids are dehydrated easily. When one mole of water is eliminated from two moles of the ortho-ic acid (intermolecular dehydration), the pyro-ic acid is formed:



Ortho-ic Acid Pyro-ic Acid

When a mole of water is eliminated from one mole of the ortho-ic acid (intramolecular dehydration), the meta-ic acid is formed:



Ortho-ic Acid Meta-ic Acid

The latter type of dehydration also occurs when the pyro-ic acid is heated. Thus, when orthophosphoric acid is heated at 250° C., it loses water to form pyrophosphoric acid, which, upon stronger heating at a higher temperature, is converted into metaphosphoric acid:

$$2H_3PO_4 \xrightarrow[(-H_2O)]{\Delta} H_2O + H_4P_2O_7 \xrightarrow[(-H_2O)]{\Delta} H_2O + 2HPO_3$$

A similar reaction occurs when ortho-arsenic acid is heated. It first loses its water of crystallization, then changes to the pyro-ic acid at around 150° C. and finally, at around 200° C., to meta-arsenic acid.

As may be seen from their structures, the pyro-ic acids of this series are tetrabasic acids, i.e., they have four acidic hydrogens, hence should form four different salts. Actually, however, only two such types of salts are known, normal salts or tetrametallic salts, such as tetrasodium pyrophosphate, $Na_4P_2O_7$, and dimetallic salts, such as disodium dihydrogen pyrophosphate, $Na_2H_2P_2O_7$.

Of the meta-ic acids, metaphosphoric acid is a glassy appearing solid, slowly soluble in water; meta-arsenic and meta-antimonic acids are also white solids. Metanitric acid can be obtained in the anhydrous state as a clear, colorless liquid but is quite unstable, decomposing into the anhydride and water. In aqueous solution, however, its decomposition is greatly decreased.

The meta-ic acids also form salts readily but, being monobasic, they form but one type, the meta-ate, as exemplified by the commonly known salts of nitric acid, the nitrates. The metaphosphates, meta-arsenates and meta-antimonates are similar in structure to the metanitrates.

Metaphosphoric acid and its salts, the metaphosphates, differ from the other meta-ic acids and the meta-ate salts of this series and from the other oxyacids of phosphorus in some unusual properties. Most outstanding of these is the strong tendency of the acid and its salts to polymerize to form polymetaphosphoric acids and polymetaphosphate salts, such as sodium hexametaphosphate, $(NaPO_3)_6$, etc. This adds to the complexity of this acid and its salts, and the structures of many of them are still not known. The acid and its salts also differ from the other phosphoric acids and their salts in their coagulating action on certain proteins, such as egg albumin, and in their ability to precipitate certain alkaloids. The latter property is sometimes made use of in the preparation and separation of single alkaloids and alkaloidal mixtures from other plant constituents.

Just as the ortho-ic acids may undergo dehydration to form the pyro-ic and meta-ic acids, so may the salts of the ortho-ic acids lose water to form salts of the pyro-ic and meta-ic acids. Thus, when monosodium dihydrogen orthophosphate is heated to about 240° C. it loses one mole of water from two moles of the salt to form disodium pyrophosphate, which, upon further heating, is converted into sodium metaphosphate:

$$2NaH_2PO_4 \xrightarrow[(-H_2O)]{\Delta} H_2O + Na_2H_2P_2O_7 \xrightarrow[(-H_2O)]{\Delta} H_2O + 2NaPO_3$$

The monosodium salt may also lose water directly within the molecule to form the corresponding sodium metaphosphate:

$$NaH_2PO_4 \xrightarrow[(-H_2O)]{\Delta} H_2O + NaPO_3$$

When disodium monohydrogen orthophosphate is heated to about 300° C., it loses one mole of water from two moles of the salt to form tetrasodium pyrophosphate:

$$2Na_2HPO_4 \xrightarrow[(-H_2O)]{\Delta} H_2O + Na_4P_2O_7$$

In a similar way, when the corresponding mixed ammonium salts are heated they lose ammonia and water to form the corresponding salt of the pyro-ic acid. Application of this behavior is made in the gravimetric assay of soluble magnesium salts, such as U.S.P. Magnesium Sulfate;[7] in this assay, insoluble magnesium ammonium phosphate is precipitated by addition of an excess of diammonium phosphate to a solution of the weighed sample:

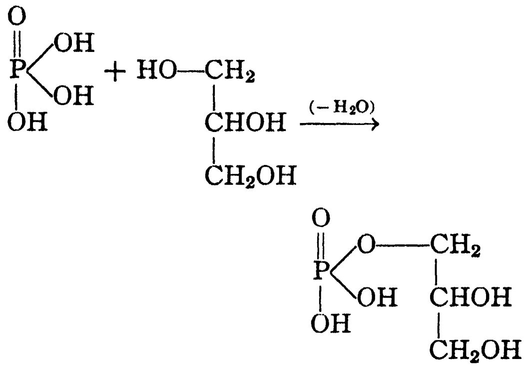
$$MgSO_4 + (NH_4)_2HPO_4 \rightarrow NH_4HSO_4 + MgNH_4PO_4$$

The precipitated magnesium ammonium phosphate is filtered, washed and ignited, losing water and ammonia and forming magnesium pyrophosphate:

$$2MgNH_4PO_4 \xrightarrow{\Delta} 2NH_3 + H_2O + Mg_2P_2O_7$$

From the weight of the magnesium pyrophosphate thus obtained the amount of magnesium sulfate in the original sample may be calculated. The same behavior is made use of in the assay of U.S.P. Sodium Phosphate[8] and other phosphate salts.

The acids of this group combine not only with metals to form salts but also with alcohols to form esters. Important compounds of this type, from a pharmaceutical viewpoint, are the esters of orthophosphoric acid with glycerol. Since glycerol is a triatomic alcohol and orthophosphoric acid is a tribasic acid, it is evident that a variety of esters of the two is possible. The one in which we are most interested is that which results from the esterification of one —OH group of the acid with one —OH group of glycerol:



Glycerophosphoric Acid

This ester is known as glycerophosphoric acid. As may be seen from its structure, it still contains two acidic hydrogens and can form salts; its salts are known as metallic glycerophosphates. A number of these are contained in the N.F. in monograph, namely, Sodium, Calcium, Manganese and Ferric Glycerophosphates. They are also contained in the N.F. Calcium and Sodium Glycerophosphates Elixir and Compound Glycerophosphates Elixir. Although the glycerophosphates still enjoy considerable use in medicine as nerve tonics and general tonics, it is doubtful that they offer any advantages over the simpler salts of phosphoric acid.

Nitric acid, like phosphoric acid, also forms esters with alcohols. Of pharmaceutical importance are the nitrate of glycerol, official in the U.S.P. as Glyceryl Trinitrate Tablets and in the N.F. as Glyceryl Trinitrate Spirit (Nitroglycerin Spirit) and used in medicine for the relief of hypertension and other pathologic heart conditions; the nitrate of erythritol, contained in the U.S.P. Erythrityl Tetranitrate Tablets; the nitrate of cellulose, contained in the U.S.P. as Pyroxylin or Soluble Guncotton. Pyroxylin is a mixture of the nitrates of cellulose, consisting chiefly of the tetranitrate, i.e., containing four nitrate radicals for each twelve carbon atoms in the cellulose molecule, $[C_{12}H_{16}O_6(NO_3)_4]_n$. The U.S.P. Col-

lodion, a solution of Pyroxylin in ether and alcohol, and Flexible Collodion, which contains castor oil and camphor in addition, are sometimes used as protective coverings for cuts and wounds. Guncotton consists chiefly of cellulose hexanitrate, $[C_{12}H_{14}O_4(NO_3)_6]_n$, and when mixed with glyceryl trinitrate (nitroglycerin), forms the well-known smokeless powder, an explosive.

The acids of this group, with the exception of phosphoric acid, are oxidizing agents, readily giving up a part of their oxygen. The oxidizing properties of nitric acid and its salts are the most marked. Nitric acid or nitrates, when mixed with substances which readily combine with oxygen (reducing agents), *may be considered* to decompose with the liberation of oxygen, which combines with the reducing agent, together with the oxides of nitrogen and water. Since the last two substances are gaseous at the temperature of the reaction, if the products of the oxidation are also gaseous an explosive mixture results. This explains why ordinary gunpowder, or black powder, is used as an explosive; it contains potassium nitrate, sulfur and charcoal in the proper proportions to yield products which are almost entirely gaseous. It also explains why nitroglycerin and guncotton are explosive while pyroxylin, the tetranitrate of cellulose, is less explosive than guncotton, the hexanitrate. In the tetranitrate, there are not sufficient nitrate groups present to completely oxidize the carbon and hydrogen to gaseous carbon dioxide and water, while in the hexanitrate, there are more than sufficient nitrate groups present to accomplish this reaction.

Nitric acid is a powerful oxidizing agent and commonly is used as such for a variety of purposes. Its action as such *may be expressed* as follows:

$$2HNO_3 \rightarrow H_2O + 2NO + 3O$$

Three atoms of oxygen are available from each two moles of the acid (p. 191). Many pharmaceutical examples of the use of nitric acid as an oxidizing agent are familiar; a few of these are cited.

1. In the preparation of ferric iron solutions, iron in the ferrous state is oxidized to the ferric state by nitric acid. Examples are found in N.F. Ferric Chloride Solution, Ferric Sulfate Solution and Ferric Subsulfate Solution (Monsel's Solution). Although the N.F. no longer contains procedures for making the first two of these, they are commonly prepared by the oxidation, by nitric acid, of ferrous chloride in the presence of hydrochloric acid and of ferrous sulfate in the presence of sulfuric acid, respectively. The N.F. still contains directions for preparing Ferric Subsulfate Solution by oxidation, with nitric acid, of ferrous sulfate in the presence of insufficient sulfuric acid to completely convert it to the ferric state[9] (p. 191). These methods of preparation explain the necessity for the N.F. to include tests for nitrate and ferrous iron impurities in these solutions.

2. In the tests for identity and purity of phosphorus, nitric acid is used to oxidize phosphorus to the pentoxide, which dissolves in water to form phosphoric acid.[10]

3. In many U.S.P. and N.F. identification tests for alkaloids, the alkaloid under examination is treated with nitric acid to oxidize it to a colored compound, thus furnishing a characteristic color reaction for the alkaloid. Examples are found under Atropine, Scopolamine Hydrobromide and others in the U.S.P. and N.F.

Application of the oxidizing action of arsenic acid in the assay of its salt, Exsiccated Sodium Arsenate N.F., where it oxidizes hydriodic acid to free iodine, has already been mentioned (p. 27).

The pentoxides of the elements of group V represent the complete dehydration products of the pentahydroxides. Phosphorus pentoxide is formed by direct union of the elements, i.e., burning phosphorus in a plentiful supply of air, which is a commercial method of preparation, while the pentoxides of the other elements are formed

by dehydration of the corresponding "-ic" acids. Thus, nitrogen pentoxide may be formed by the dehydrating action of phosphorus pentoxide on nitric acid; arsenic and antimony pentoxides may be obtained by subjecting their hydrates to dull, red-heat. Bismuth pentoxide has not been obtained in the pure state. Pure phosphorus pentoxide is a white, odorless compound, usually without definite crystalline form. Arsenic pentoxide is white, while antimony pentoxide is pale yellow; both are usually amorphous.

Nitrogen pentoxide, at low temperatures, is a white, crystalline compound but is unstable, readily decomposing into nitrogen dioxide and oxygen. In fact, all of the pentoxides of this group, except phosphorus pentoxide, are unstable and readily give up part of their oxygen to revert to the trioxides; thus, they act as oxidizing agents.

The most characteristic property of phosphorus pentoxide is the ease with which it takes up water, this property making it a valuable drying and dehydrating agent. The other pentoxides are hydrated only with much more difficulty.

Uses. For industrial purposes, nitric acid is the most widely used of the acids of this group. It is used in the manufacture of inorganic nitrates, sulfuric acid and other chemicals and in the preparation of explosives, dyes and plastics. Large quantities are used as an oxidizing agent and as a nitrating agent in the preparation of organic nitrates and nitro compounds.

Orthophosphoric acid finds its greatest industrial use in the manufacture of fertilizers. Arsenic and antimonic acids find little use as such in industry.

Table 29 gives the forms in which these acids and their dehydration products are contained in the U.S.P. and N.F.

Nitric acid is seldom used internally in medicine, although Diluted Nitrohydrochloric Acid finds some use for the same purposes as hydrochloric acid (p. 46) and as a hepatic stimulant; its value as the latter is doubtful. Exernally, nitric acid is used as an escharotic for the removal of warts, corns and other such tissue; great care should be exercised in its use for this purpose because of its destructive action on normal tissue. It has its greatest use as an oxidizing and nitrating agent in the laboratory.

Orthophosphoric acid has some medicinal use as a tonic and gastric stimulant. It is also widely used along with various flavoring agents in the preparation of refrigerant phosphate beverages. It is commonly used in the laboratory as a general analytical reagent and in the preparation of dental cements. Metaphosphoric acid also is used for the latter purpose as well as a coagulating reagent in testing for albumin.

Arsenic and antimonic acids have no use as such in medicine. These acids, as well as nitric and phosphoric acids, have more uses

Table 29. U.S.P. and N.F. Forms of the Pentahydroxides of Group V

Name	Type of Preparation	Strength
Phosphoric Acid, U.S.P. Reagent	Aqueous	85-88 per cent
Phosphoric Acid N.F.	Aqueous	85-88 per cent
Diluted Phosphoric Acid N.F.	Aqueous	10 per cent
Metaphosphoric Acid, U.S.P. Reagent (Glacial Phosphoric Acid)	....	Pure
Phosphorus Pentoxide, U.S.P. Reagent	....	Pure
Arsenic Pentoxide, N.F. Reagent	....	Pure
Nitric Acid, Fuming, U.S.P. Reagent	....	....
Nitric Acid N.F.	Aqueous	67-71 per cent
Nitrohydrochloric Acid N.F. (Aqua Regia; Nitromuriatic Acid)	Aqueous-HCl	....
Diluted Nitrohydrochloric Acid N.F.	Aqueous-HCl	....

in pharmacy and medicine in the form of their salts, which will be considered in the next section.

Salts of the Acids

As previously mentioned, the ortho-ic acids, being tribasic, form three types of salts. The pyro-ic acids, although they are tetrabasic, form only two types of salts, i.e., dimetallic and tetrametallic; while the meta-ic acids, being monobasic, form only one type of salt.

The Ortho-ate Salts. Practically all of the alkali metal salts of phosphoric acid are made by neutralization of the acid by the corresponding alkali hydroxide, the salt formed depending upon the extent of neutralization (p. 170). The various calcium salts are made by the action of a calculated quantity of sulfuric acid on tricalcium orthophosphate, while the other metallic phosphates, such as those of magnesium, aluminum, ferric iron, etc., are commonly made by double decomposition between a soluble sodium phosphate and a soluble salt of the metal concerned. The alkali metal salts of arsenic acid are usually made by oxidation of the corresponding trivalent arsenic compound, and the other metallic arsenates may be made by double decomposition between a soluble sodium arsenate and a soluble salt of the metal concerned.

The physical and chemical properties of the metallic phosphates and arsenates are very similar. Only the mono-, di- and trialkali metallic arsenates and phosphates are freely soluble in water and, of these, the phosphates are more soluble than the arsenates. The mono-alkaline earth metallic phosphates are also water-soluble, although less so than the alkali phosphates. The primary alkali phosphates of the formula $M'H_2PO_4$ are always acid in reaction, while the secondary alkali phosphates, M'_2HPO_4, are strongly hydrolyzed in solution and show an even greater alkaline reaction than the tertiary salts, M'_3PO_4. Because of this property, monosodium dihydrogen orthophosphate is frequently used to insure an acid medium for the proper release and action of medicinal agents. An example of this is found in the N.F. Tablets of Methenamine and Sodium Biphosphate; methenamine is effective as a urinary antiseptic only in an acid medium. Both the monosodium and disodium salts, as well as the corresponding potassium salts, are also used in buffer solutions for the control of the hydrogen ion concentration.

The phosphates and arsenates of the heavy metals are insoluble in water, but are soluble in weak acids, in dilute mineral acids and in ammonia. Use is made of this property in the U.S.P. identification tests for soluble arsenates and orthophosphates, the insoluble silver arsenate or phosphate produced by the addition of silver nitrate being soluble in dilute nitric acid and in ammonia, T.S.[11]

The phosphate and arsenate radicals have no color themselves, and most of their salts are colorless. Some of their insoluble salts, however, possess color. Thus, silver phosphate is yellow, ferric phosphate is cream-colored and silver arsenate is reddish-brown or chocolate brown.[11]

The phosphates of the ammonium ion and a metal other than an alkali metal are often particularly insoluble. The quantitative application of this property of magnesium ammonium phosphate in the assay of soluble magnesium salts as well as some phosphates has already been cited (p. 172). Magnesium ammonium arsenate is similarly insoluble and is useful in the detection and estimation of soluble arsenates in the same way.[11]

The action of heat on the salts of orthophosphoric acid has been mentioned (p. 171). Elimination of water to yield first the pyro- and finally the meta-ate takes place in the same way with the ortho-arsenates but with much more ease than is the case with the orthophosphates. Both the trimetallic phosphates and arsenates are stable toward heat.

In the following list is given the most

commonly known salts of orthophosphoric and ortho-arsenic acids, together with their common names and uses. Many of these are contained in the U.S.P. or N.F. in monograph form or as reagents.

A. Monometal Dihydrogen Ortho-ates of the Formula $M'H_2PO_4$ or $M''(H_2PO_4)_2$.

Sodium Biphosphate U.S.P., $NaH_2PO_4 \cdot H_2O$ (Sodium Dihydrogen Phosphate, Monosodium Orthophosphate, Sodium Acid Phosphate, Primary Sodium Phosphate), is used to furnish an acid medium in the urinary tract, and also as a constituent of some baking powders.

Potassium Biphosphate, U.S.P. Reagent, KH_2PO_4 (Monopotassium Phosphate, Monobasic Potassium Phosphate, etc.), is used chiefly in buffer solutions for the control of pH.

Ammonium Phosphate, Monobasic, $NH_4H_2PO_4$ (Ammonium Biphosphate, Ammonium Dihydrogen Phosphate, Primary Ammonium Phosphate), is used with sodium bicarbonate as a constituent of some baking powders. It also is used as a source of phosphorus and nitrogen in culture media for yeasts and bacteria and industrially as a fireproofing agent. A recent industrial use of crystals of this salt, under the designation PN and also ADP, for converting vibratory mechanical energy into corresponding electrical energy and vice versa has grown out of its use by the Navy during World War II in underwater sound equipment.[12]

Calcium Biphosphate, U.S.P. Reagent, $Ca(H_2PO_4)_2 \cdot H_2O$ (Calcium Phosphate, Monobasic; Calcium Acid Phosphate; Monocalcium Phosphate; Primary Calcium Phosphate), is used chiefly in fertilizers as a plant food and with sodium bicarbonate in baking powders. Since rock phosphate, tricalcium orthophosphate, is practically insoluble, its use as a fertilizer is accompanied by the disadvantage that it is very slowly absorbed by the plant. Consequently, a "Superphosphate" or "Superphosphate of Lime" fertilizer is made by the action of a calculated quantity of sulfuric acid on rock phosphate to yield a mixture of the more soluble calcium biphosphate and gypsum:

$$Ca_3(PO_4)_2 + 2H_2SO_4 + 4H_2O \rightarrow Ca(H_2PO_4)_2 + 2CaSO_4 \cdot 2H_2O$$

An even stronger "Triple Superphosphate" fertilizer is made by using orthophosphoric acid:

$$Ca_3(PO_4)_2 + 4H_3PO_4 \rightarrow 3Ca(H_2PO_4)_2$$

B. Dimetal Monohydrogen Ortho-ates of the Formula M'_2HPO_4, M'_2HAsO_4, $M''HPO_4$, etc.

Sodium Phosphate U.S.P., $Na_2HPO_4 \cdot 7H_2O$ (Dibasic Sodium Phosphate, Disodium Orthophosphate, Disodium Hydrogen Phosphate, Secondary Sodium Phosphate), also is present as the anhydrous salt in Exsiccated Sodium Phosphate U.S.P., in Effervescent Sodium Phosphate U.S.P., in Sodium Phosphate Solution N.F. and in Sodium Phosphate, Dibasic, N.F. Reagent. It is used as a pleasant tasting saline cathartic, especially in the form of the solution and the effervescent salt. This salt crystallizes from water in two different forms; the dodecahydrate, $Na_2HPO_4 \cdot 12H_2O$, crystallizes from cold solutions, the heptahydrate, $Na_2HPO_4 \cdot 7H_2O$, from solutions above a temperature of 35° C. The latter form, which is the one official in the U.S.P., is therefore almost half water. The crystals effloresce in the air, especially in warm, dry air and should be preserved in an airtight container.[13] If the salt has undergone extensive efflorescence, the average dose of 4 Gm. may actually contain almost double that amount of anhydrous salt. In preparing the U.S.P. Exsiccated Sodium Phosphate, the heptahydrate is allowed to effloresce in dry air for several days before it is heated in an oven to remove the remaining water. This is done in order to slowly remove most of the large quantity of water of crystallization, which would otherwise be removed too rapidly, causing the salt to dissolve in its own water of crystallization upon being heated. In such an event the hard glassy mass re-

sulting upon evaporation would still contain some water which could be removed only with difficulty. The exsiccated salt absorbs moisture from the air and must be stored in airtight containers; otherwise the average dose of 2 Gm. would contain less of the anhydrous salt than is intended.[14]

Potassium Phosphate, Dibasic, U.S.P. Reagent, K_2HPO_4 (Dipotassium Phosphate, Secondary Potassium Phosphate, Potassium Phosphate), is used chiefly in buffer solutions for control of pH.

Ammonium Phosphate, Dibasic, U.S.P. Reagent, $(NH_4)_2HPO_4$ (Diammonium Hydrogen Phosphate, Secondary Ammonium Phosphate), is used as a diuretic and saline cathartic in conditions of rheumatism and gout and also as a source of phosphorus and nitrogen in culture media for yeasts and bacteria. Industrially it is used as a fertilizer and fireproofing agent for fabrics.

Sodium Ammonium Phosphate, U.S.P. Reagent, $NaNH_4HPO_4 \cdot 4H_2O$ (Microcosmic Salt), is used in blowpipe analysis in a bead test similar to the borax bead.

Dibasic Calcium Phosphate U.S.P., $CaHPO_4 \cdot 2H_2O$ (Dicalcium Orthophosphate, Secondary Calcium Phosphate), is one of the most important calcium salts from the standpoint of pharmaceutical and medicinal interest. It is used in medicine as a mineral food to supply calcium and phosphorus in conditions of rickets, osteomyelitis, anemia, dental caries, etc. It is used especially as an ingredient of mineral supplements for swine, cattle and other animals. It is used as an abrasive agent in tooth powders and is of some use as an antacid and hemostatic agent.

Exsiccated Sodium Arsenate N.F., Na_2HAsO_4 (Dibasic Sodium Arsenate, Disodium Ortho-arsenate), also is contained in 1 per cent solution in the N.F. Sodium Arsenate Solution. It is used in medicine as an alterative in conditions of functional neuroses, pernicious anemia, malaria, etc. A sweetened solution is also used as a fly-killer. It is used industrially in the dyeing and printing of fabrics.

Lead Arsenate, $PbHAsO_4$, is used as a constituent of insecticidal powders and sprays.

C. Trimetal Ortho-ates of the Formula M'_3PO_4, M'_3AsO_4, $M''_3(PO_4)_2$, $M'''PO_4$, etc.

Trisodium Orthophosphate, $Na_3PO_4 \cdot 12H_2O$ (Sodium Phosphate, Tribasic; Trisodium Phosphate; Normal Sodium Phosphate; Tertiary Sodium Phosphate), is used as a detergent and water softener in cleansing mixtures, laundries, etc.; it also is used in photographic developers and in various industries. In aqueous solution it is strongly alkaline because of hydrolysis to disodium monohydrogen orthophosphate and sodium hydroxide.

Tribasic Calcium Phosphate N.F., $Ca_3(PO_4)_2$ (Precipitated Calcium Phosphate, Tricalcium Phosphate, Tertiary Calcium Phosphate, Normal Calcium Phosphate), is used in medicine and pharmacy for much the same purposes as the dicalcium salt.

Tribasic Magnesium Phosphate N.F., $Mg_3(PO_4)_2 \cdot 5H_2O$ (Tertiary Magnesium Phosphate, Normal Magnesium Phosphate, also in the N.F. Tribasic Magnesium Phosphate Tablets), is used commonly as an antacid agent in conditions of gastric hyperacidity, peptic ulcers, etc.

Aluminum Phosphate Gel U.S.P. is a colloidal suspension containing 3.8 to 4.5 per cent of $AlPO_4$ and usually containing flavoring, sweetening and preservative agents in addition. It is used for its antacid, astringent and adsorbent properties in conditions of gastric hyperacidity, peptic ulcers, etc. Aluminum Phosphate, Tribasic Calcium Phosphate and Tribasic Magnesium Phosphate have the advantage over alkaline hydroxides and carbonates such as magnesium hydroxide, sodium bicarbonate, etc., in that, being less soluble, they tend to neutralize only the excess acidity of the stomach without producing systemic alkalization. In addition, the demulcent and adsorbent proper-

ties of Aluminum Phosphate Gel make it of value in providing a protective lining over ulcerated areas and protecting them from other irritation.

Soluble Ferric Phosphate N.F. (Ferric Phosphate with Sodium Citrate) is ferric phosphate rendered soluble by the presence of sodium citrate; it is used as a hematinic.

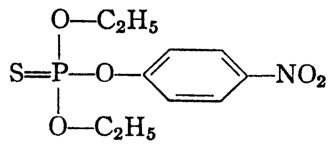
The Pyro-ate Salts. The alkali metal salts of pyrophosphoric acid may be made by the action of heat on the corresponding metallic orthophosphate (p. 171) or by the neutralization of pyrophosphoric acid itself. The pyrophosphates of other metals may be made by double decomposition between a soluble sodium pyrophosphate and a soluble salt of the metal concerned.

Both the dimetallic and the tetrametallic pyrophosphates of alkali metals are soluble in water; only the dimetallic pyrophosphates of the other metals are water-soluble. The insoluble pyrophosphates of the other metals, however, will dissolve in an excess of alkali pyrophosphate, with the formation of complex compounds.

The pyrophosphate salts have little or no use in medicine. Ferric pyrophosphate, $Fe_4(P_2O_7)_3 \cdot 9H_2O$, was last included in the N.F. VII as Soluble Ferric Pyrophosphate, in combination with sodium citrate, as one of the scale salts of iron. Tetrasodium Pyrophosphate, $Na_4P_2O_7 \cdot 10H_2O$, N.F. Reagent, has been used as a mild cathartic, like Sodium Phosphate U.S.P., and sometimes is used to stabilize hydrogen peroxide solutions. It has its greatest use as a water softening agent, by forming soluble complexes with the magnesium and calcium salts in hard water and thus preventing the precipitating action of these salts on soap. Disodium dihydrogen pyrophosphate, sodium acid pyrophosphate, $Na_2H_2P_2O_7$, is used in some baking powders. The importance of magnesium pyrophosphate, $Mg_2P_2O_7$, in gravimetric analysis has already been mentioned (p. 172).

An ester of pyrophosphoric acid, tetraethyl pyrophosphate, commonly known as TEP, recently has assumed importance as an insecticide in the control of aphids and mites, against which DDT is ineffective.[15] It is claimed to be more toxic as an insecticide than hexaethyl tetraphosphate, the agent developed in Germany as a substitute for nicotine and now being produced in this country as an insecticide.[16] In fact, recent evidence has shown that the insecticidal ingredient in the so-called hexaethyl tetraphosphate is actually tetraethyl pyrophosphate.[17] Hexaethyl tetraphosphate is apparently the ester of tetraphosphoric acid, $H_6P_4O_{13}$, which is made up of four phosphoric acids linked in the same way as in pyrophosphoric acid.

An ester of thiophosphoric acid, diethyl-*p*-nitro phenylthiophosphate,



(Parathion, Thiophos 3422, E605), first developed in Germany, also is being produced commercially as an insecticide.[18]

The pyro-arsenates and pyro-antimonates are analogous to the pyrophosphates in preparation and properties. None of these has medicinal uses. Dipotassium dihydrogen pyro-antimonate, potassium acid pyro-antimonate, $K_2H_2Sb_2O_7 \cdot 6H_2O$, has been used as a reagent for the qualitative detection of sodium, the corresponding sodium salt of pyro-antimonic acid being the least soluble sodium salt known.

The Meta-ate Salts. The metaphosphate salts are commonly prepared by heating together calculated amounts of phosphoric acid and the corresponding metallic oxide as well as by dehydration of the corresponding monometal dihydrogen orthophosphate or dimetal dihydrogen pyrophosphate (p. 172). The nature and complexity of the metaphosphate resulting from the latter method of preparation are dependent upon the conditions of heating during the dehydration. The metaphosphates of the alkali

metals are soluble in water, and their strong tendency to polymerize and form complex salts has been mentioned (p. 171). The alkali polymetaphosphates also have the ability to form soluble complexes with other metals; advantage is taken of this property in the use of sodium hexametaphosphate, as a water-conditioning agent in the prevention of carbonate scale formation in boilers, treatment of water in laundries, etc. It forms soluble complexes with the calcium and magnesium salts present in hard water, as does tetrasodium pyrophosphate, to reduce their concentration to such an extent that soaps are not precipitated by these ions. The metaphosphates have no use in medicine or pharmacy except as occasional reagents.

The metallic nitrates, metanitrates, are almost all prepared by the action of nitric acid on the corresponding metal, metallic oxide or carbonate, or by the action of a mixture of the oxides of nitrogen and air on the same substances. Other nitrates may be made by double decomposition reactions.

All of the metallic nitrates are readily soluble in water; even lead, which forms insoluble salts with most inorganic acids, forms a soluble nitrate. They are much more soluble in hot water than in cold, and this property is used, for example, in preparing potassium nitrate from the corresponding naturally occurring sodium salt by reaction with potassium chloride:

$$KCl + NaNO_3 \rightleftharpoons NaCl + KNO_3$$

In the mixture of products present in this reversible reaction, sodium chloride is the least soluble on heating, while potassium nitrate is the least soluble in the cold. By using hot concentrated solutions of sodium nitrate, the sodium chloride can be made to separate out of the hot solution; it is removed by filtration, and the potassium nitrate then crystallizes out upon cooling.

The nitrate radical itself is without color; hence, the nitrates of colorless ions are colorless, while the nitrates of colored ions retain that color, e.g., ferric nitrate is pale violet, cupric nitrate is blue, etc. The metallic nitrates and halates, in which halogen exhibits the same pentavalence as nitrogen, are analogous in many of their properties, e.g., nitrates and chlorates are isomorphous.

TABLE 30. COMMONLY KNOWN SALTS OF NITRIC ACID

NAME	FORMULA	USE
Sodium Nitrate (Chile Saltpeter)	$NaNO_3$	Diuretic, diaphoretic
Potassium Nitrate N.F. (Saltpeter)	KNO_3	Diuretic, diaphoretic
Ammonium Nitrate, U.S.P. Reagent	NH_4NO_3	Making nitrous oxide, pyrotechnics, fertilizer
Silver Nitrate U.S.P.	$AgNO_3$	External germicide, caustic, analytical reagent
Toughened Silver Nitrate U.S.P. (Lunar Caustic)	$AgNO_3(+AgCl)$	External caustic
Mercurous Nitrate, U.S.P. Reagent	$HgNO_3 \cdot H_2O$	Antiseptic, caustic
Barium Nitrate, U.S.P. Reagent	$Ba(NO_3)_2$	Making pyrotechnics, reagent
Lead Nitrate, U.S.P. Reagent	$Pb(NO_3)_2$	External antiseptic, astringent, making explosives, mordant
Mercuric Nitrate Ointment N.F. (Citrine Ointment)	....	External antiseptic, stimulant in various skin diseases
Cobalt Nitrate, N.F. Reagent	$Co(NO_3)_2 \cdot 6H_2O$	Pigment, HCN antidote
Bismuth Subnitrate N.F.	(See p. 183)	Internal astringent, antiseptic and protective
Thorium Nitrate, U.S.P. Reagent	$Th(NO_3)_4 \cdot H_2O$	External astringent, reagent

The nitrates are unstable to high temperatures, and the products of decomposition upon heating are dependent upon the metal concerned. Thus, alkali metal nitrates, such as potassium or sodium, liberate oxygen and form the corresponding nitrite at red-heat (p. 93); heavy metal nitrates, such as lead or copper, liberate oxygen, nitrogen dioxide and form the metallic oxide; ammonium nitrate decomposes into water and nitrous oxide (p. 191).

In Table 30 above are given the most commonly known salts of metanitric acid, together with their common names and uses. Many of these are contained in the U.S.P. or N.F. in monograph form or as reagents.

TRIHYDROXIDES

The Acids

With ₦ as the general symbol for the elements of group V acting in their trivalent state, the following trihydroxides and their partial and complete dehydration products, together with their names, are indicated as follows:

Representatives of almost all of the compounds listed in the above table are commonly known. Unlike the pentahydroxides, the trihydroxides of the elements of group V, with the exception of that of nitrogen, are more stable; hence the ortho-ous acids and their salts, the ortho-ites, are as well-known as the meta-ous acids and their salts, the meta-ites. Orthonitrous acid is not commonly known; metanitrous acid is not too stable but its salts are well known.

Occurrence. Neither the trihydroxides of the elements of group V nor their partial dehydration products occur in the free state in nature. With the exception of phosphorous acid, none of them commonly exists in the free, anhydrous condition but only in solution with much water or in combination as salts. Occurrence of their salts in nature is rare. The complete dehydration products of some of them, viz., the trioxides of arsenic, antimony and bismuth, occur rather commonly among ores containing these elements.

Methods of Formation and Preparation.

₦$(OH)_3$ Trihydroxide (ortho-ous acid)	₦O·OH Monoxide-monohydroxide (meta-ous acid)	₦$_2O_3$ Trioxide ("-ous" Acid Anhydride)
$N(OH)_3$ Orthonitrous acid	NO·OH * Metanitrous acid	N_2O_3 Nitrogen trioxide (Nitrous acid anhydride)
$P(OH)_3$ Orthophosphorous acid	PO·OH Metaphosphorous acid	P_2O_3 Phosphorus trioxide (Phosphorous acid anhydride)
$As(OH)_3$ * Ortho-arsenous acid	AsO·OH * Meta-arsenous acid	As_2O_3 * Arsenic trioxide (Arsenous acid anhydride)
$Sb(OH)_3$ Ortho-antimonous acid	SbO·OH * Meta-antimonous acid	Sb_2O_3 Antimony trioxide (Antimonous acid anhydride)
$Bi(OH)_3$ * Orthobismuthous acid	BiO·OH Metabismuthous acid	Bi_2O_3 Bismuth trioxide (Bismuthous acid anyhdride)

* Compounds that are of pharmaceutical importance and are represented in the U.S.P. or N.F., either as such or in the form of their salts.

I. Hydration of the Oxide.

$$N_2O_3 + H_2O \rightarrow 2NO{\cdot}OH$$

or

$$N_2O_3 + 3H_2O \rightarrow 2N(OH)_3$$

Hydration of the trioxides of the elements of group V will form either the meta-ous acid or the ortho-ous acid, depending upon the extent of the reaction.

A. $N_2O_3 + H_2O \rightarrow 2HNO_2$

Hydration of nitrogen trioxide will yield metanitrous acid, but this is not a method of preparation since nitrogen trioxide is not stable.

B. $P_2O_3 + H_2O \rightarrow 2HPO_2$

$P_2O_3 + 3H_2O \rightarrow 2H_3PO_3$

Like the pentoxide, phosphorus trioxide combines very actively with water to form the phosphorous acids.

C. $As_2O_3 + H_2O \rightarrow 2HAsO_2$

$As_2O_3 + 3H_2O \rightarrow 2H_3AsO_3$

One or both of these reactions undoubtedly take place to a certain extent when arsenic trioxide is dissolved in water with the aid of hydrochloric acid, as in the preparation of N.F. Arsenious Acid Solution.[19] Other reactions, in addition to the above, probably take place (p. 182).

Hydration of arsenic trioxide also occurs when it is dissolved in water with the aid of an alkali, such as potassium bicarbonate; this happens in the preparation of U.S.P. Potassium Arsenite Solution (Fowler's Solution).[20] In this case, however, the potassium salts are formed as a result of the neutralization of the arsenous acids. Which arsenous acids and which potassium salts are present in this product is not known; it is probably a mixture of all of them, including potassium meta-arsenite, $KAsO_2$, the mono-, di- and tripotassium ortho-arsenites, KH_2AsO_3, K_2HAsO_3 and K_3AsO_3, respectively, and even possibly some of the dipotassium pyro-arsenite, $K_2H_2As_2O_5$.

D. $Sb_2O_3 + H_2O \rightarrow 2HSbO_2$

$Sb_2O_3 + 3H_2O \rightarrow 2H_3SbO_3$

Antimony trioxide is practically insoluble in water. However, in the presence of sufficient hydrochloric acid it will dissolve, presumably largely as the chloride, from which solution there is precipitated white, amorphous antimonous acid, H_3SbO_3 (probably a mixture of this with the oxychloride), by the addition of a large volume of water.

II. Action of Acid upon a Suitable Salt.

$$2M'NO_2 + H_2SO_4 \rightarrow M'_2SO_4 + 2HNO_2$$

This reaction occurs with the liberation of nitrous acid in the assays of the U.S.P. Sodium Nitrite and Potassium Nitrite; the nitrous acid is then determined by oxidation with N/10 $KMnO_4$ (p. 97).

In the same way, in the organic chemistry laboratory, nitrous acid is liberated for the diazotization of primary aromatic amines by the action of hydrochloric acid upon sodium nitrite. A quantitative application of this reaction is found in the assay of the U.S.P. Sulfanilamide[21] and the other sulfonamide drugs of the U.S.P. and N.F. by measuring the amount of nitrous acid or sodium nitrite required to completely diazotize the weighed sample of the sulfonamide.

III. Hydrolysis of an Ester of the Acid.

$$R{-}O{-}N{=}O + H_2O \rightarrow ROH + HNO_2$$

Esters of nitrous acid, the alkyl nitrites, are subject to hydrolysis on standing, with the liberation of nitrous acid, and this is a common cause of their deterioration. This property explains in part the necessity for the U.S.P. and N.F. to include tests for free acid in Amyl Nitrite and Ethyl Nitrite Spirit, respectively.[22]

Hydrolysis of the esters also occurs in the nitrite assay procedure of the U.S.P. and N.F. by which the above two esters are assayed. The nitrous acid thus liberated

then may be determined either gasometrically or iodometrically (p. 27).

IV. Reduction of the Corresponding "-ic" Acid.

$$H_3AsO_4 + 2HI \rightarrow I_2 + H_2O + H_3AsO_3$$

This method of formation of arsenous acid has already been mentioned (p. 27) as occurring in the assay of N.F. Exsiccated Sodium Arsenate; measurement of the amount of iodine liberated in this quantitative reaction, by titration with N/10 $Na_2S_2O_3$, gives a measure of the amount of sodium arsenate present in the weighed sample taken for assay.

V. Hydrolysis of the Halide.

$$NX_3 + 3H_2O \rightarrow 3HX + N(OH)_3$$

A. $PBr_3 + 3H_2O \rightarrow 3HBr + P(OH)_3$

$$PI_3 + 3H_2O \rightarrow 3HI + P(OH)_3$$

This has been mentioned previously (p. 41) as one of the chief methods for the preparation of hydrobromic and hydriodic acids in the laboratory. When the gaseous hydrogen halide passes out of the reaction mixture, a solution of orthophosphorous acid remains behind.

B. 1. $AsI_3 + 3H_2O \rightarrow 3HI + As(OH)_3$

When arsenic tri-iodide dissolves in water, there is obtained, not a simple solution of AsI_3 in water, but largely a mixture of hydriodic acid and ortho-arsenous acid (p. 40). In this case the hydrolysis reaction proceeds almost entirely to completion because the hydriodic acid, in the presence of atmospheric oxygen, is oxidized to free iodine and water, thus removing or altering irreversibly one of the reaction products.

2. $AsCl_3 + 3H_2O \rightarrow 3HCl + As(OH)_3$

When arsenic trioxide is dissolved in water with the aid of hydrochloric acid, as is the case in the preparation of N.F. Arsenious Acid Solution (p. 181), the above reaction is undoubtedly among those taking place. When the trioxide is dissolved, arsenic trichloride is formed, at least in part:

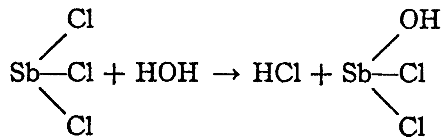
$$As_2O_3 + 6HCl \rightarrow 3H_2O + 2AsCl_3$$

and the arsenic trichloride is hydrolyzed by the excess water present to form ortho-arsenous acid. These are reversible reactions and are governed by the law of mass action. Since there is an excess of water present, the hydrolysis probably proceeds to a great extent; however, since all of the products remain in solution, an equilibrium among the four substances is undoubtedly established.

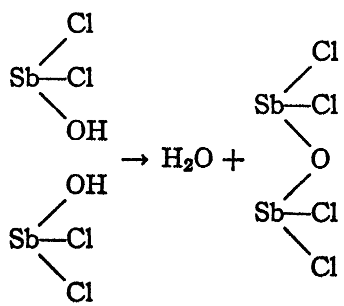
C. $SbCl_3 + 3H_2O \rightarrow 3HCl + Sb(OH)_3$

Like the analogous reaction between arsenic trichloride and water, this is also a reversible reaction, the direction and extent to which it proceeds depending upon the relative amounts of water and hydrochloric acid present. In this case, however, there is opportunity for the formation of insoluble compounds which are removed from the field of action and thus change the course of the reaction.

Thus, for example, when a little water and much hydrochloric acid are present, the hydrolysis may proceed to only a slight extent:

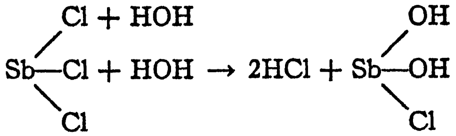


The compound, $Sb(OH)Cl_2$, being insoluble, might be precipitated or two moles of it might interact with the elimination of water:

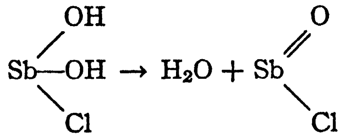


forming another insoluble antimony oxychloride.

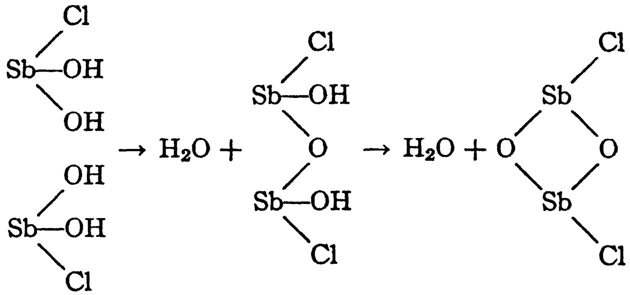
With more water added to a solution of $SbCl_3$ further hydrolysis might take place:



The oxychloride, $Sb(OH)_2Cl$, thus formed might be precipitated or it might lose water within itself



or between two moles:



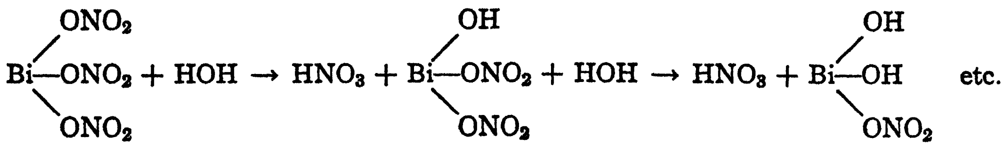
and so on to form other insoluble oxychlorides of antimony.

In this way, by varying the relative quantities of water and acid, the above oxychlorides of antimony, plus a considerable number of others, may be formed. The behavior of antimony trichloride with water and hydrochloric acid is thus explained, as is also the behavior of antimony trioxide when dissolved in hydrochloric acid and the solution is diluted with water. Long boiling with large amounts of water would presumably completely hydrolyze the antimony trichloride to ortho-antimonous acid and antimony trioxide. Antimony trichloride itself, commonly known as Butter of Antimony because of its former butyraceous appearance, is a colorless, crystalline solid which fumes slightly in the air, due to partial hydrolysis. It was formerly official in various pharmacopeias and is still carried in stock in some drug stores for use largely in veterinary medicine. The mixture of oxychlorides of antimony, prepared as shown above, was formerly in medical favor under the name, Powder of Algaroth, named after Vitorrio Algarotto, an Italian physician of the late sixteenth century.

VI. Hydrolysis of a Salt Other than the Halide. This method, which is closely allied to the one discussed in V above, is applicable only to the more basic members of the "-ous" acids, i.e., those which form salts with acids. It is of special interest and importance with reference to the medicinal compounds and preparations of bismuth.

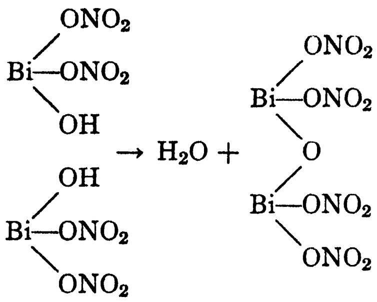
$$\text{A. } Bi(NO_3)_3 + 3H_2O \rightarrow 3HNO_3 + Bi(OH_3)$$

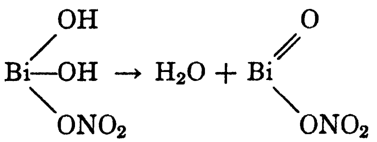
This reaction, like those between the trihalides and water, is reversible, the direction and extent to which it proceeds depending upon the relative amounts of water and acid present. Bismuth nitrate is not soluble in water unless an excess of nitric acid is present because of the formation of insoluble basic bismuth nitrates by the hydrolytic action of water:

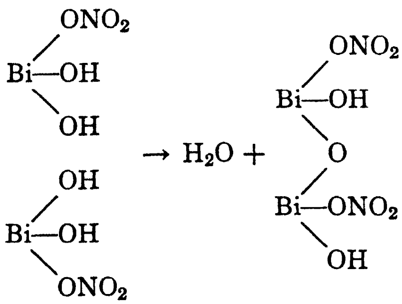


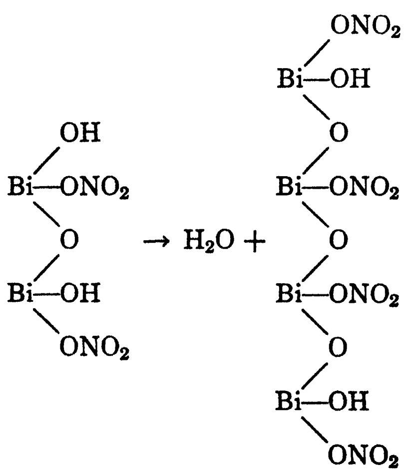
As with the corresponding oxychlorides of antimony, water may be eliminated from

the above compounds to give other basic bismuth nitrates:









and so on, forming a complex mixture of basic nitrates which are known as bismuth subnitrates. The official Bismuth Subnitrate of the N.F.[23] is a mixture of such compounds which yields, upon ignition, not less than 79 per cent of Bi_2O_3. According to the earlier editions of the U.S.P., to as late as that of 1870, this product was prepared by the action of water on crystalline bismuth nitrate. If the hydrolysis proceeds far enough, i.e., by continuous removal of the nitric acid formed and addition of large amounts of water, orthobismuthous acid, $Bi(OH)_3$, and bismuth trioxide, Bi_2O_3, would be obtained. In the presence of an acid, i.e., HCl or HNO_3, the above reactions are reversed and the insoluble basic salts are converted into soluble normal salts of bismuth, thus explaining the solubility behavior of the N.F. product.[23]

B. $Bi_2(CO_3)_3 + 6H_2O \rightarrow 3H_2CO_3 + 2Bi(OH)_3$

The U.S.P. Bismuth Subcarbonate[24] is prepared by treating a normal bismuth salt, such as bismuth nitrate, with a solution of an alkaline carbonate, such as sodium carbonate, and washing and drying the resulting precipitate. In this way, a mixture of basic bismuth carbonates of varying composition, depending upon the conditions of precipitation and washing, is obtained. If the precipitate is washed for too long a period or with too much water, there is a possibility of hydrolyzing the subcarbonates completely to the trihydroxide or trioxide. Some of the reactions that may be assumed to take place in its preparation can be indicated. By double decomposition, the normal bismuth carbonate might be formed:

$$2Bi(NO_3)_3 + 3Na_2CO_3 \rightarrow 6NaNO_3 + Bi_2(CO_3)_3$$

In the process of washing this would undergo partial hydrolysis, with the formation of basic carbonates:

$$Bi_2(CO_3)_3 + 2H_2O \rightarrow Bi_2(OH)_2(CO_3)_2$$

$$\xrightarrow{+2H_2O} Bi_2(OH)_4CO_3 \xrightarrow{-2H_2O} Bi_2O_2CO_3$$

and so on, the extent to which the hydrolysis proceeds depending on the conditions observed. The U.S.P. requires the product to

yield not less than 90 per cent Bi_2O_3 upon ignition. It is soluble in acids, i.e., HCl and HNO_3, with effervescence, forming carbonic acid and the soluble normal salt of bismuth.[24]

C. The N.F. Bismuth Subgallate (Dermatol) is prepared by the reaction between gallic acid and normal bismuth nitrate in glacial acetic acid solution. In this preparation, a mixture of the subgallates of bismuth, of varying composition depending upon the conditions observed in the procedure, is obtained. The official product is required to yield between 52 and 57 per cent of Bi_2O_3 upon ignition. It is soluble with decomposition in acids, forming soluble gallic acid and the soluble normal salt of bismuth.[25]

D. The U.S.P. Bismuth Subsalicylate is prepared by reaction between hydrated bismuth trioxide or bismuth trihydroxide and salicylic acid and consists of a mixture of the subsalicylates of bismuth of varying composition. The official product is required to yield between 62 and 66 per cent of Bi_2O_3 upon ignition. It is insoluble in cold water and reacts with mineral acids to form the soluble normal bismuth salt and insoluble salicylic acid.[26]

E. The N.F. Bismuth Magma is prepared by reaction of bismuth nitrate and ammonium carbonate.[27] Bismuth Subnitrate is first treated in aqueous suspension with nitric acid in order to convert it into the soluble normal bismuth nitrate. This solution then is added to an aqueous solution of ammonium carbonate and ammonium hydroxide, the resulting precipitate is washed with water until free from ammonium nitrate and ammonium hydroxide (until the washings are no longer pink to phenolphthalein), and then the magma is made up to specified volume with water. The N.F. describes this preparation as an aqueous suspension of bismuth hydroxide and bismuth subcarbonate yielding, upon drying and ignition, between 5.2 and 5.8 per cent of Bi_2O_3. The reactions occurring in this method of preparation may be indicated in part as follows:

$$2Bi(NO_3)_2 + 3(NH_4)_2CO_3 \rightarrow 6NH_4NO_3 + Bi_2(CO_3)_3$$

The bismuth carbonate thus formed is then partially hydrolyzed during the washing to the basic bismuth carbonates as shown in B above. At the same time, bismuth trihydroxide is formed by reaction of the ammonium hydroxide on bismuth nitrate:

$$Bi(NO_3)_3 + 3NH_4OH \rightarrow 3NH_4NO_3 + Bi(OH)_3$$

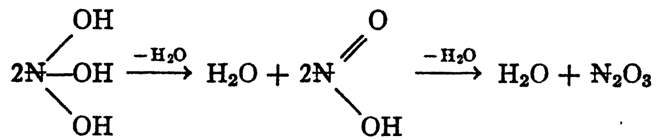
However, these reactions probably do not represent the whole picture of what takes place. It is assumed here that, in the presence of the alkali, any subnitrates that are formed are hydrolyzed almost completely to the trihydroxide, with the formation of ammonium nitrate which is removed during the subsequent washing of the precipitate.

Properties. Unlike the pentahydroxides of this group, which, because of their instability, are not commonly known, the trihydroxides or ortho-ous acids are the commonly known compounds. Orthonitrous acid is the only exception; its partial dehydration product, metanitrous acid, is more commonly known but only in the form of a dilute aqueous solution as well as in the form of its salts, the nitrites. The free acid decomposes into water and nitrogen trioxide, or nitrous anhydride, which immediately decomposes further into nitric oxide and nitrogen dioxide:

$$2HNO_2 \rightarrow H_2O + [N_2O_3] \rightarrow NO + NO_2$$

Phosphorous acid is known as such in the form of a colorless, crystalline solid when pure. Arsenous acid is known only in aqueous solution since it is easily dehydrated to form arsenic trioxide. A true antimonous acid probably never has been prepared, although a hydrated antimony trioxide in the form of a white solid has been obtained; it is readily dehydrated to the trioxide. Bismuthous acid is not known as such.

In general, the ortho-ous acids of the elements of Group V are more "acid" in character than are the corresponding ortho-ic acids in which the element is pentavalent. Like the "-ic" acids, with an increase in the atomic weight of the element, i.e., with the change from nonmetallic to metallic character, the acidic character of the "-ous" acids decreases, from nitrogen to bismuth, with a corresponding increase in their basic character. Thus, while nitrous and phosphorous acids exhibit only acidic properties and form salts with metallic ions (e.g., nitrites and phosphites), arsenous, antimonous and bismuthous acids are amphoteric compounds and may react either as acids or bases. Arsenous acid functions more frequently as an acidic substance, forming metallic arsenites of the formula $M'AsO_2$, M'_3AsO_3, etc. While antimonous acid and bismuthous acid will form metallic antimonites, $M'SbO_2$, M'_3SbO_3, etc., and metallic bismuthites, $M'BiO_2$, M'_3BiO_3, etc., with strong alkalies, such salts are not commonly known. On the other hand, antimonous acid and, more frequently, bismuthous acid act as bases and form salts with acids; e.g.,

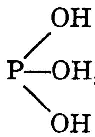


Ortho-ous Acid — Meta-ous Acid — "-ous" Acid Anhydride

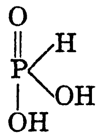
salts like antimony nitrate, $Sb(NO_3)_3$, and bismuth nitrate, $Bi(NO_3)_2$, are commonly known. Also, compounds like the U.S.P. Antimony Potassium Tartrate (Tartar Emetic)[28] and Bismuth Potassium Tartrate[29] furnish examples of antimonous acid and bismuthous acid acting as bases (although the latter is probably not a pure compound).

Like the ortho-ic acids, the ortho-ous acids have three acidic hydrogens and hence are capable of forming three types of salts or ortho-ites, depending upon whether one, two or all three hydrogens are replaced by metal. Representative examples of most of these salts are known, as well as representative salts of the meta-ous acids. The nomenclature of the ortho-ite salts is the same as for the corresponding ortho-ate salts.

Orthophosphorous acid is somewhat anomalous in that, while it contains three hydrogens and its structure is commonly considered to be



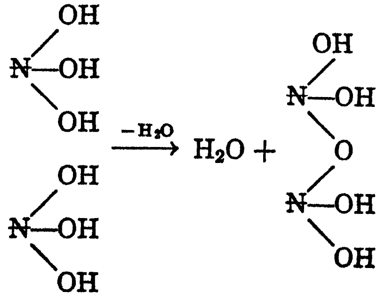
it reacts as a dibasic acid, forming salts like M'_2HPO_3, and indicating that its structure conforms more closely to



in which phosphorus is pentavalent. The fact that phosphorous acid is a stronger acid than phosphoric acid also lends credence to the latter structure.

Like the ortho-ic acids, the ortho-ous acids also exhibit the property of losing water by intramolecular dehydration to form the corresponding meta-ous acids and finally the "-ous" acid anhydride or trioxide:

Under different conditions they may lose water by intermolecular dehydration to form the pyro-ous acids:



Ortho-ous Acid — Pyro-ous Acid

As may be seen from the above structure, the pyro-ous acid thus formed has four acidic hydrogens, i.e., it is a tetrabasic acid, hence is theoretically capable of forming four series of salts. Some of the salts of pyrophosphorous, pyro-arsenous and pyro-antimonous acids, $H_4P_2O_5$, $H_4As_2O_5$ and $H_4Sb_2O_5$, respectively, are known. Also known are salts, such as $Na_2As_4O_7$, which represent a polyarsenous acid formed by dehydration between four moles of ortho-arsenous acid:

$$4H_3AsO_3 \xrightarrow{-5H_2O} 5H_2O + H_2As_4O_7$$

Such a salt is analogous in formula to the salts of the poly-acids of the elements of group III, such as Sodium Borate, $Na_2B_4O_7$, the salt of tetraboric acid (p. 236).

The "-ous" acids and their salts of this group act as reducing agents by taking on oxygen, with the element changing in valence from three to five, and being oxidized to the corresponding "-ic" acid. Examples of the reducing action of the "-ous" acids have already been cited under the methods of formation of the "-ic" acids and elsewhere. Thus, in the assay of the U.S.P. Potassium Nitrite and Sodium Nitrite, the nitrous acid, liberated from the salts by action of sulfuric acid, is oxidized by N/10 $KMnO_4$ to nitric acid (p. 97). In the assay of the trivalent arsenic compounds of the U.S.P. and N.F., including Arsenic Trioxide, Arsenious Acid Solution, Potassium Arsenite Solution, Arsenic Triiodide and others, arsenous acid is oxidized by N/10 Iodine to arsenic acid, the iodine being reduced at the same time to hydrogen iodide (p. 40). In the assay of the U.S.P. Antimony Potassium Tartrate, analogous reactions take place between antimonous acid and iodine (p. 40).

Metanitrous acid can act not only as a reducing agent but as an oxidizing agent as well. In the presence of substances having a strong affinity for oxygen *it may be considered* to decompose as follows:

$$2HNO_2 \rightarrow H_2O + [N_2O_3] \rightarrow NO + [NO_2] \rightarrow NO + O$$

The oxygen thus liberated exerts its oxidizing action. Thus, with hydrogen iodide or its salts, nitrous acid or nitrites, in the presence of a mineral acid, oxidize the hydrogen iodide to water and free iodine:

$$2HI + 2HNO_2 \rightarrow 2H_2O + 2NO + I_2$$

This reaction forms the basis for the iodometric method of assay of nitrites by the N.F. procedure, the amount of iodine liberated being quantitatively determined by titration with N/10 $Na_2S_2O_3$ (p. 27). It is also the basis for the U.S.P. identification test for nitrites.[80]

Nitrous acid may even be said to oxidize itself. Thus, under certain conditions it decomposes with the formation of nitric acid and nitric oxide:

$$3HNO_2 \rightarrow HNO_3 + H_2O + 2NO$$

This decomposition may be assumed to take place by the oxidation of one mole of nitrous acid at the expense of two other moles, the oxygen liberated by decomposition of the two moles being sufficient to oxidize a third mole of nitrous acid to nitric acid:

$$2HNO_2 \rightarrow H_2O + 2NO + O$$
$$HNO_2 + \tfrac{1}{2}O_2 \rightarrow HNO_3$$

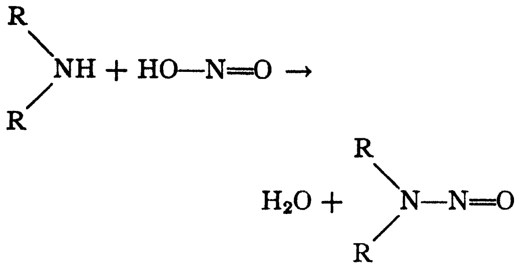
Nitrous acid also exhibits other properties not commonly exhibited by the other "-ous" acids of this group. With ammonia, it reacts to form free nitrogen and water:

$$HO\text{—}N\text{=}O + H_2NH \rightarrow H_2O + [HO\text{—}N\text{=}NH] \rightarrow H_2O + N_2$$

With monosubstituted ammonias, i.e., primary aliphatic amines, a similar reaction takes place with the formation of an alcohol:

$$HO\text{—}N\text{=}O + H_2N\text{—}R \rightarrow H_2O + [HO\text{—}N\text{=}N\text{—}R] \rightarrow R\text{—}OH + N_2$$

With secondary amines, an oily nitroso amine is formed:



These reactions are used in organic chemistry as a means of distinguishing between primary and secondary amines. With primary aromatic amines, nitrous acid reacts to form the valuable diazonium salts which are intermediates in the preparation of organic dyes and other organic medicinal agents:

$$Ar—NH_2 \cdot HCl + HO—N{=}O \rightarrow 2H_2O + Ar—N_2Cl$$

These latter properties of nitrous acid are more properly considered in greater detail in courses in organic chemistry.

Trioxides

The trioxides of the elements of group V, which represent the complete dehydration products of the trihydroxides, may be formed, in the case of some, by direct union of the element with oxygen; in the case of others, by oxidation of the trisulfide. All of them may be prepared by dehydration of the corresponding ortho-ous or meta-ous acid.

As an example of the first method, when phosphorus is allowed to stand in contact with the air or when it is heated in a limited supply of air, phosphorus trioxide is formed along with the pentoxide (p. 152). Likewise, arsenic, antimony and bismuth, when heated in contact with the air, are oxidized to their trioxides (p. 153).

An example of the oxidation of the trisulfide is furnished in the preparation of arsenic trioxide by the roasting of its trisulfide ore (p. 150). Most of the commercial product is produced by the roasting of such arsenical ores as arsenical pyrites:

$$FeS_2 \cdot FeAs_2 + 5O_2 \xrightarrow{\Delta} Fe_2O_3 + 2SO_2 + As_2O_3$$

The impure arsenic trioxide which collects in the flue dust of these smelters is purified further by resublimation.

A pharmaceutical example of this method of formation is found in the procedure by which the U.S.P. Sublimed Sulfur and Precipitated Sulfur are treated in testing them for arsenic impurity.[31] Any arsenic impurity in these products is present as the trisulfide (p. 121). By digestion with ammonia it is rendered soluble (p. 198) and filtered from the insoluble sulfur; upon evaporation of the filtrate, with the addition of nitric acid, the arsenic trisulfide is oxidized to the trioxide while at the same time the sulfur, which would interfere in the subsequent test for arsenic, is removed by being converted to volatile sulfur dioxide.

Examples of the formation of the trioxides by dehydration of the ortho-ous and meta-ous acids have already been mentioned under the properties of these acids (p. 185). In most instances the trihydroxides exist only in aqueous solution or as hydrated trioxides, and dehydration occurs almost spontaneously with attempts to isolate the hydroxide. This is especially true of nitrous acid; when it is formed by action of an acid upon a nitrite salt it immediately is dehydrated to nitrogen trioxide, N_2O_3, which further breaks down immediately, liberating nitric oxide, NO, and nitrogen dioxide, NO_2. The former, escaping into the air, is oxidized to form more nitrogen dioxide which appears as reddish-brown fumes. These reactions form the basis of one of the U.S.P. identification tests for nitrite and may be shown as follows:[32]

$$2M'NO_2 + 2H^+ \rightarrow 2M^+ + 2HNO_2$$
$$2HNO_2 \rightarrow H_2O + [N_2O_3] \rightarrow NO_2 + NO$$
$$2NO + O_2 \rightarrow 2NO_2$$

However, if potassium iodide is added, the nitrogen dioxide will oxidize the hydrogen

iodide to free iodine, which will give a blue color with starch; this furnishes a second identification test for nitrite (p. 187) and also serves as an indicator in the U.S.P. assay of sulfanilamide and its derivatives.

An equimolecular mixture of nitric oxide and nitrogen dioxide can be condensed to nitrous anhydride when cooled to low temperatures, but it immediately decomposes when the temperature is raised. When dissolved in water, nitrogen trioxide yields a mixture of nitrous and nitric acids, but with alkali, it combines only to yield a metallic nitrite. This apparently anomalous behavior may be explained by considering the fact that nitrous acid, as an oxidizing agent, may oxidize itself (p. 187):

$$2N_2O_3 + 2H_2O \rightarrow 4HNO_2$$

$$3HNO_2 \rightarrow HNO_3 + H_2O + 2NO$$

or, by writing the two above reactions as one:

$$2N_2O_3 + H_2O \rightarrow HNO_2 + HNO_3 + 2NO$$

The other trioxides of this group are solids of various crystalline or amorphous modifications. Phosphorus trioxide may be obtained as white, monoclinic prisms. Arsenic trioxide exists in different forms, of which the amorphous and the octahedral forms are most common. Antimony trioxide is a white powder, while bismuth trioxide is a cream-colored or light yellow powder. Phosphorus trioxide possesses a garliclike odor and is poisonous, as is arsenic trioxide, which is commonly used as a constituent of rodent poisons. Arsenic trioxide is commonly known as Arsenious Acid and as White Arsenic.[33]

The chemical properties of the trioxides are the same as those of the "-ous" acids, into which the trioxides are converted by hydration. The ease of hydration of the trioxides decreases with an increase in the atomic weight of the element concerned. Thus, phosphorus trioxide slowly reacts with water to form phosphorous acid, arsenic trioxide is very slowly soluble in water, antimony trioxide is very sparingly soluble and bismuth trioxide is insoluble in water.

Phosphorus trioxide is unstable in the air and is readily oxidized to the pentoxide. It ignites spontaneously in oxygen. The other trioxides are more stable in this respect; in fact, the trioxides of arsenic, antimony and bismuth are more stable than their pentoxides.

Salts of the Acids

As previously mentioned, the ortho-ous acids, being tribasic, form three types of salts, while the meta-ous acids, being monobasic, form only one type of salt. Salts of the pyro-ous acids are of no pharmaceutical importance. Generally speaking, the salts of the "-ous" acids are not of as much interest in pharmacy and medicine as are the salts of the "-ic" acids of the elements of group V.

Since nitrous acid is a fairly weak acid and its salts are susceptible to hydrolysis, only the salts of the more strongly metallic elements, i.e., alkali and alkaline earth metals, are commonly known. A few exceptions to this are noted among the nitrites of mercury and silver. The metallic nitrites may be made by reduction of the corresponding nitrate by heat alone or with the aid of reducing agents, or, in the case of mercurous nitrite, by the action of dilute nitric acid and nitrogen dioxide on the metal. Double decomposition reactions may also be employed to prepare one metallic nitrite from another. The alkali and alkaline earth nitrites are white compounds and are freely soluble in water, while the nitrites of other metals, i.e., silver and mercury, are yellow in color and are much less soluble in water. All of the metallic nitrites, except that of silver, are hygroscopic. They all liberate nitrous acid when acted on by acids and also yield nitrous acid by hydrolysis of their solutions, especially when boiled. Ammonium nitrite is especially unstable and decomposes, even at room temperature and in aqueous solution, into nitrogen and water.

Only the alkali metal salts of arsenous acid are soluble in water and these are very strongly hydrolyzed, their solutions being alkaline in reaction. The arsenites of the heavy metals are insoluble in water but are soluble in an excess of alkali. Application of the insolubility of ferric arsenite is made in the use of ferric hydroxide as an antidote for arsenic poisoning. Magma of Ferric Hydroxide (Arsenic Antidote), last official in the U.S.P. XI, a suspension made by reaction between ferric sulfate and magnesium oxide,[84] is an example of such a preparation. Some authorities claim, however, that the arsenic, instead of forming a compound with the ferric hydroxide, is adsorbed on the surface of the suspended particles and that the association takes place by surface action.[85]

Uses of the Acids and Their Compounds

Nitrous acid as such has no use in pharmacy or medicine. Many of the uses of nitrous acid, liberated by the action of an acid on its salts, as a reagent in the laboratory have been cited under its properties. The nitrite ion acts as a vasodilator, causing a fall in blood pressure, and is of value in the relief of hypertension in certain conditions of heart spasms and asthmatic attacks. It also acts as a diuretic and diaphoretic. The U.S.P. Amyl Nitrite and the N.F. Ethyl Nitrite Spirit (Spirit of Nitrous Ether, Sweet Spirit of Nitre) both elicit these responses. Sodium Nitrite U.S.P. and Potassium Nitrite, U.S.P. Reagents, are more commonly used as reagents than as medicinal agents.

Arsenous acid, in the U.S.P. Arsenious Acid Solution and Arsenic Trioxide and in the N.F. Potassium Arsenite Solution (Fowler's Solution), is used in medicine as an alterative and tonic in various conditions. The mono copper ortho-arsenite salt, $As(OH)(O_2Cu)$, commonly known as Scheele's Green, is a well-known pigment, while Paris Green, a mixed salt or mixture of salts of cupric ortho-arsenite and cupric acetate, generally written as $(AsO_3)_2Cu_3 \cdot (CH_3COO)_2Cu$, is a well-known insecticide. Arsenites of sodium and calcium are also used, along with the corresponding arsenates of these metals and lead, as constituents of insecticidal mixtures.

Antimonous acid is contained, in combination, in the U.S.P. Antimony Potassium Tartrate which has lost favor as an emetic but still has considerable use in small doses as an expectorant. It also has been somewhat useful in the treatment of various tropical infections. Its bismuth counterpart, the U.S.P. Bismuth Potassium Tartrate, has some use in the treatment of syphilis and other infections.

Bismuth Magma of the N.F. is a commonly used intestinal astringent. The various bismuth subsalts or oxysalts have already been mentioned (p. 183). Of these, Bismuth Subcarbonate and Bismuth Subnitrate are used especially as antacids and astringents internally, and both internally and externally as dusting powders and protective agents. Bismuth Subgallate and Bismuth Subsalicylate are used as intestinal astringents and antiseptics; the former is also used externally as an absorbent and protective in dusting powders, while the latter has been used some as an antisyphilitic.

OXIDES OTHER THAN N_2O_5 AND N_2O_3

Oxides, other than the pentoxides and trioxides already discussed, are known for all of the elements of group V. Of the other oxides, however, only those of nitrogen are of pharmaceutical interest and will be considered here. A list of the commonly known oxides of nitrogen is as follows:

N_2O, Nitrous Oxide
NO, Nitric Oxide
N_2O_3, Nitrogen Trioxide
NO_2, Nitrogen Dioxide
N_2O_4, Nitrogen Tetroxide
N_2O_5, Nitrogen Pentoxide

NITROUS OXIDE, N_2O

This compound, the Nitrous Oxide of the U.S.P., is also known as Nitrogen Monoxide and as "laughing gas." It was first made in 1772 by Priestley by the action of moist iron filings on nitric oxide:

$$2NO + H_2O + Fe \rightarrow Fe(OH)_2 + N_2O$$

Nitrous oxide is made commercially by heating ammonium nitrate (p. 180) or by heating a mixture of sodium and potassium nitrates with ammonium sulfate:

$$NH_4NO_3 \xrightarrow{\Delta} 2H_2O + N_2O$$

Nitrous oxide is a colorless gas with a slightly sweet odor and taste. It is quite soluble in water but does not, however, combine chemically with water to form an oxyacid as do the other oxides of nitrogen; its aqueous solution is neutral to litmus. The gas is easily liquefied at −89.5° C. and solidifies to colorless crystals at −102.3° C. Its critical temperature is 35° C. Hence, for convenience in storage and handling, it usually appears on the market compressed in metal cylinders.[86]

Chemically, nitrous oxide may be regarded as the theoretical anhydride of hyponitrous acid, and in aqueous solution this acid slowly decomposes into nitrous oxide and water:

$$H_2N_2O_2 \rightarrow H_2O + N_2O$$

The reverse of this reaction, however, i.e., hydration of nitrous oxide to hyponitrous acid, will not occur.

Nitrous oxide readily parts with its oxygen, hence it is an oxidizing agent and will support combustion like oxygen. When a glowing splinter is thrust into it, the splinter burns as it would in oxygen, although not as briskly:

$$2N_2O + C \rightarrow CO_2 + 2N_2$$

It will not, however, support respiration like oxygen, and when used as an anesthetic, oxygen is usually administered along with it.

Nitrous Oxide U.S.P. is used as a gaseous anesthetic in minor surgery and dentistry. Inhalation of too large an amount of it will produce toxic symptoms and death. Its common name, laughing gas, comes from the characteristic exhilarating and sometimes hysteric symptoms which it produces in some patients after it is inhaled in small amounts.

NITRIC OXIDE, NO

This oxide of nitrogen is formed under many different conditions, all of which may be summarized chiefly under three general methods, namely: reduction of nitric acid, decomposition of nitrous acid or a nitrite and direct union of nitrogen and oxygen.

When nitric acid acts on such metals as copper, silver or mercury, nitric oxide gas is liberated:

$$3Cu + 8HNO_3 \rightarrow 3Cu(NO_3)_2 + 4H_2O + 2NO$$

It combines immediately with oxygen of the air to form the reddish-brown fumes of nitrogen dioxide:

$$2NO + O_2 \rightarrow 2NO_2$$

The same reaction occurs when a nitrate is heated with sulfuric acid and copper and is used as one of the U.S.P. tests for identity of nitric acid and nitrates.[87]

Nitric oxide is formed in the manufacture of pharmaceutical preparations where nitric acid is used as an oxidizing agent as, for example, in the oxidation of ferrous salts to the ferric state. Thus, in the preparation of N.F. Ferric Subsulfate Solution (p. 138) the following reaction may be assumed to occur in part:

$$2HNO_3 + 6FeSO_4 + 3H_2SO_4 \rightarrow 3Fe_2(SO_4)_3 + 4H_2O + 2NO$$

A similar reaction occurs in the oxidation of ferrous chloride in the preparation of the N.F. Ferric Chloride Solution:

$$2HNO_3 + 6FeCl_2 + 6HCl \rightarrow 6FeCl_3 + 4H_2O + 2NO$$

The nitric oxide gas, escaping in each case, again combines with the oxygen of the air to form reddish-brown fumes of nitrogen dioxide.

Nitric oxide is also formed by the decomposition of nitrous acid and when nitrous acid or a nitrite act as oxidizing agents. These properties and reactions have already been discussed (p. 187). If a reducing agent is present, e.g., hydrogen iodide, the nitrogen dioxide resulting from the nitrous acid will oxidize it to free iodine, being itself reduced to nitric oxide. If no reducing agent is present, the nitrogen dioxide escapes into the air as reddish-brown fumes and this latter behavior furnishes another U.S.P. test for the identity of nitrites.[37]

Finally, nitric oxide may be formed by the direct union of nitrogen and oxygen, as is the case in the commercial production of nitric acid (p. 167) from the nitrogen and oxygen of the air; it may be formed by the catalytic oxidation of ammonia, by which process nitric acid is also produced. The former is known as the electric arc process. The electric arc discharge produces the high temperature necessary for nitrogen and oxygen to combine:

$$N_2 + O_2 \xrightarrow{\Delta} 2NO - 43 \text{ Cal.}$$

Nitric oxide is produced only in about two and one-half per cent yield in this way; the process is not efficient and is little used at present.

The catalytic oxidation of ammonia constitutes the well-known Ostwald Process. A mixture of 10 per cent ammonia in air is preheated to approximately 600° C. and passed over platinum gauze at a temperature of 900-1,000° C. After the reaction has started, its strongly exothermic nature furnishes enough energy to keep it going without the application of further heating:

$$4NH_3 + 5O_2 \rightarrow 6H_2O + 4NO + 215 \text{ Cal.}$$

The nitric oxide thus produced is oxidized by excess oxygen to nitrogen dioxide, which is then hydrated by hot water to nitric acid:

$$2NO + O_2 \rightarrow 2NO_2 + 27.8 \text{ Cal.}$$

$$3NO_2 + H_2O \xrightarrow{\Delta} 2HNO_3 + NO$$

The nitric oxide resulting from this hydration is used again in the process.

Nitric oxide is a colorless gas, sparingly soluble in water at ordinary temperatures and difficult to liquefy. It is noncombustible and very stable to heat, being dissociated into nitrogen and oxygen only at high temperatures. As already mentioned, it combines readily with more oxygen to form nitrogen dioxide and is easily oxidized by other oxidizing agents as well.

Nitric oxide dissolves readily in solutions of ferrous salts to form a dark-brown colored solution of a complex ion. This property forms the basis of a delicate test for the presence of nitrates, since ferrous salts in the presence of free acid readily reduce nitrates or nitric acid to nitric oxide, which then gives the brown-colored solution with the excess of the ferrous salt. This is another one of the U.S.P. tests for identity of nitrates.[37]

Nitrogen Dioxide, NO_2, and Nitrogen Tetroxide, N_2O_4

Nitrogen dioxide, NO_2, is formed, as shown in the previous discussion, when nitrous acid decomposes and when nitric acid or a nitrate act as oxidizing agents. Nitric acid to which has been added nitrogen dioxide is known as red nitric acid or fuming nitric acid because of its color and is an even more rapid oxidizing agent than nitric acid itself. Nitrogen dioxide may also be formed by the action of heat on the nitrates of heavy metals (p. 180):

$$2Pb(NO_3)_2 \xrightarrow{\Delta} 2PbO + O_2 + 4NO_2$$

It is a dark reddish-brown gas, of strong pungent odor, and is poisonous. It can be condensed to a pale yellow liquid, and at still lower temperatures to a colorless solid.

Nitrogen dioxide and nitrogen tetroxide

apparently exist in an equilibrium mixture, the content of which is dependent upon the temperature. Thus, at low temperatures, the tetroxide predominates and it passes into the dioxide upon raising the temperature:

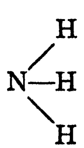
$$N_2O_4 \rightleftharpoons 2NO_2$$

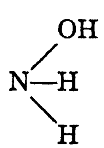
Nitrogen tetroxide may be regarded as the theoretical mixed anhydride of nitrous acid and nitric acid, and when the gas reacts with water at low temperatures, it is hydrated to a mixture of nitrous and nitric acids:

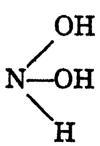
$$N_2O_4 + H_2O \rightarrow HNO_2 + HNO_3$$

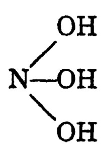
MIXED HYDRIDE-HYDROXIDES OF THE ELEMENTS OF GROUP V

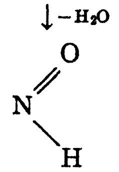
There are a number of both basic and acidic compounds of the elements of Group V which do not appear to fit into the systematic scheme of the hydrides or the hydroxides as it has been developed up to this point. However, if we take the point of view of the organic chemist, who regards organic compounds as hydrocarbons (hydrides of carbon) and their substitution products, we may account in a rational manner for a number of these compounds which may otherwise appear to be irregular. Thus, taking the trihydride of nitrogen as the parent compound, its mono-, di- and tri-hydroxy substitution products may be systematized as follows:

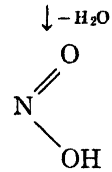

Trihydride (Ammonia)


Monohydroxy Derivative (Hydroxylamine)


Dihydroxy Derivative

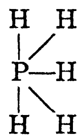

Trihydroxy Derivative (Orthonitrous Acid)

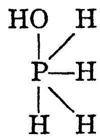

(Hypothetical Monomer of Hyponitrous Acid)

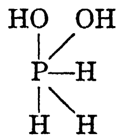

(Metanitrous Acid)

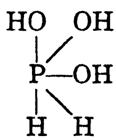
From the above diagram of the hydroxy substitution products of nitrogen trihydride it may be seen how hydroxylamine, already discussed (p. 162), fits logically into the scheme. This scheme of mixed hydride-hydroxides of the elements of group V in their trivalent state will not be developed further since none of the other intermediate products are known.

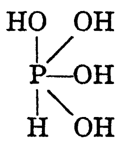
The value of such an approach readily becomes apparent when it is applied to the elements in their pentavalent state and especially in the case of phosphorus. Taking the hypothetical pentahydride of phosphorus as the parent compound, the corresponding hydroxy substitution products and their dehydration products may be shown as follows:

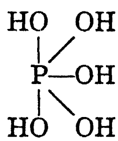

Pentahydride (Hypothetical)

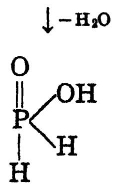

Monohydroxy Derivative (Phosphonium Hydroxide)

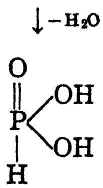

Dihydroxy Derivative

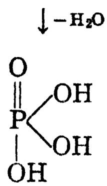

Trihydroxy Derivative


Tetrahydroxy Derivative


Pentahydroxy Derivative


Hypophosphorous Acid, H_3PO_2


Phosphorous Acid, H_3PO_3


Orthophosphoric Acid, H_3PO_4

From the above it may be seen how hypophosphorous acid fits logically into the scheme of mixed hydride-hydroxides of phosphorus; furthermore, it may be seen how phosphorous acid, already mentioned as showing anomalous properties as a trihydroxide (p. 186), fits into this scheme. This approach will not be developed further, for the mixed hydride-hydroxides of the other elements of group V since none of them, if they are known, is of importance in pharmacy.

Hypophosphorous acid, H_3PO_2, is so named because it contains less oxygen, in proportion to phosphorus, than does the corresponding phosphorous acid, H_3PO_3. This is another example of the same type of nomenclature in inorganic chemistry that has already been exhibited among the oxyacids of the halogens, e.g., perchloric, chloric, chlorous and hypochlorous acids; among the oxyacids of sulfur, e.g., persulfuric, sulfuric, sulfurous and hyposulfurous acids and among the oxyacids of other elements.

Hypophosphorous acid is found in the U.S.P. in monograph as Hypophosphorous Acid, a preparation containing 30 to 32 per cent of the acid in aqueous solution. Several of its salts are in the N.F. in monograph, in the hypophosphites of Sodium, Potassium, Calcium, Manganese and ferric iron. The acid and its salts also enter into several of the official preparations, hypophosphorous acid being used in the U.S.P. Diluted Hydriodic Acid, the N.F. Ferrous Iodide Syrup, and its various salts in the N.F. Hypophosphites Syrup and Compound Hypophosphites Syrup. The presence of the ammonium salt is also allowed in the N.F. Ammonium Iodide as a stabilizing agent.

The hypophosphite salts of the alkali and alkaline earth metals are commonly prepared by boiling yellow phosphorus with a solution of the corresponding metallic hydroxide (p. 156). Thus, the hypophosphites of sodium, potassium, calcium and barium may be prepared:

$$3M'OH + 4P + 3H_2O \xrightarrow{\Delta} PH_3 + 3M'H_2PO_2$$

or

$$3M''(OH)_2 + 8P + 6H_2O \xrightarrow{\Delta} 2PH_3 + 3M''(H_2PO_2)_2$$

If the free acid is desired, the barium salt may be treated with an equivalent quantity of sulfuric acid and the insoluble barium sulfate can be removed by filtration:

$$Ba(H_2PO_2)_2 + H_2SO_4 \rightarrow BaSO_4 + 2H_3PO_2$$

or the calcium salt may be treated with an equivalent quantity of oxalic acid and the insoluble calcium oxalate removed by filtration. These methods of preparation explain the necessity for the U.S.P. tests for barium and for oxalate as possible impurities in the acid.[38]

Ammonium hypophosphite may be prepared by neutralizing the acid with ammonia, while ferric hypophosphite and manganese hypophosphite are conveniently prepared by double decomposition reactions between calcium hypophosphite and ferric chloride and manganous sulfate, respectively. The hypophosphites of sodium and potassium may also be prepared by reaction of calcium hypophosphite with the corresponding metallic carbonate.

Hypophosphorous acid is a colorless, syrupy liquid, freely soluble in water, which can be solidified on cooling to a crystalline solid melting at 26.5° C. It acts as a monobasic acid, forming only one type of salt, and, like phosphorous acid, is more strongly acid in character than orthophosphoric acid. Its alkali and alkaline earth metal salts are soluble in water.

Both hypophosphorous acid and its salts decompose upon heating, with the liberation of phosphine. From hypophosphorous acid, besides phosphine, phosphorous acid is also obtained:

$$3H_3PO_2 \xrightarrow{\Delta} PH_3 + 2H_3PO_3$$

With metallic hypophosphites, besides phos-

phine, the salt of either orthophosphoric acid or pyrophosphoric acid (depending upon the amount of heat applied) is also obtained:

$$2M'H_2PO_2 \xrightarrow{\Delta} PH_3 + M'_2HPO_4$$

or

$$4M'H_2PO_2 \xrightarrow{\Delta} 2PH_3 + H_2O + M'_4P_2O_7$$

This property of the salts is used as one of the U.S.P. tests for identifying hypophosphites.[39]

Hypophosphorous acid and its salts are very strong reducing agents, being oxidized at the same time to orthophosphoric acid or its salts. Thus, in the presence of sulfuric acid, the free acid or its salts will decolorize potassium permanganate solution immediately. They will also reduce mercuric chloride to white, insoluble mercurous chloride:

$$4HgCl_2 + H_3PO_2 + 2H_2O \rightarrow 4HgCl + 4HCl + H_3PO_4$$

and, if an excess is added, will further reduce the mercurous chloride to gray metallic mercury:

$$4HgCl + H_3PO_2 + 2H_2O \rightarrow 4Hg + 4HCl + H_3PO_4$$

This property is the basis of another U.S.P. test for identity of hypophosphites.[39] The reducing property of the hypophosphite salts is also reflected in the precaution stated in the N.F. that explosions may occur if they are triturated or heated with nitrates, chlorates or other oxidizing agents.[40]

The strong reducing action of hypophosphorous acid and its salts has other pharmaceutical applications. Thus, for example, the U.S.P. Diluted Hydriodic Acid contains hypophosphorous acid to prevent the atmospheric oxidation of the hydrogen iodide to free iodine or to reduce back to hydrogen iodide any free iodine formed by such oxidation. Solutions containing hydrogen iodide are very readily oxidized by atmospheric oxygen, with the liberation of free iodine, because of the strongly exothermic nature of the reaction (p. 26):

$$4HI\ aq. + O_2 \rightarrow 2H_2O\ liq. + 2I_2 + 82.8\ Cal.$$

By the same token, the reverse of this reaction, reduction of iodine to hydrogen iodide, is as strongly endothermic. However, the oxidation of hypophosphorous acid is so much more strongly exothermic that its presence in the preparation induces the reduction of any free iodine that may have been formed by atmospheric oxidation of the hydrogen iodide:

$$2I_2 + 2H_2O\ liq. \rightarrow 4HI\ aq. + O_2 \quad - 82.8\ Cal.$$

$$H_3PO_2\ aq. + O_2 \rightarrow H_3PO_4\ aq. \quad +167.8\ Cal.$$

$$\text{net energy change} \quad + 85.0\ Cal.$$

As may be seen from these thermochemical equations, the sum total of the two reactions is strongly exothermic. For the same purpose, i.e., to prevent or overcome atmospheric oxidation, hypophosphorous acid is included in N.F. Ferrous Iodide Syrup[41] and not more than one per cent of ammonium hypophosphite is allowed in N.F. Ammonium Iodide.[42]

The method of assay of the hypophosphite salts of the N.F., with the exception of Ferric Hypophosphite, is also based on the strong reducing action of hypophosphorous acid. In the assay of Calcium Hypophosphite, for example, hypophosphorous acid, liberated from a weighed sample of the salt by the action of sulfuric acid, is allowed to reduce the bromine in a measured excess of N/10 bromine solution (p. 31), and the amount of hypophosphite present in the sample is calculated in terms of the number of cc. of N/10 bromine to which it is equivalent.[43] The essential reactions involved for purposes of calculation may be shown as follows:

$$Ca(H_2PO_2)_2 + H_2SO_4 \rightarrow CaSO_4 + 2H_3PO_2$$

$$2Br_2 + 2H_2O + H_3PO_2 \rightarrow 4HBr + H_3PO_4$$

The medicinal use of the various hypophosphite salts, although somewhat popular formerly as general nerve tonics and alteratives, is of doubtful efficacy.

THIOHYDROXIDES OF THE ELEMENTS OF GROUP V

In addition to the hydroxides and oxides of the elements of group V, there are the corresponding compounds in which sulfur takes the place of oxygen. These are the sulfhydrides or thiohydroxides and the sulfides of the elements of group V. These compounds are analogous to the hydroxides and oxides, not only in their structure and composition, but also in their methods of formation and preparation and in their properties. Some of them, especially those of arsenic, have pharmaceutical significance.

Pentathiohydroxides

With Ꞥ as the general symbol for the elements of group V in their pentavalent state, the following pentathiohydroxides and their partial and complete desulfhydration products, together with the names, are indicated in tabular form.

Trithiohydroxides

With Ꞥ as the general symbol for the elements of group V in their trivalent state, the trithiohydroxides and their partial and complete desulfhydration products, together with the names, are indicated on page 197.

Of the compounds listed in the two tables, none is contained in the U.S.P. or N.F., although some of them are formed in various tests for identity and purity and in the manufacture of some pharmaceutical preparations.

Compounds of nitrogen with sulfur have been prepared but they are not stable and are not commonly known. A number of compounds of phosphorus with sulfur have been prepared by heating the two elements in various proportions. Compounds of phosphorus with sulfur may occur in nature. In the preparation of phosphorus from the bones of animals some sulfur may appear in the finished product in the form of phosphorus sulfides. The N.F. VII includes a test for sulfur as impurity in Phosphorus.[44] Sulfur, if present, is oxidized by nitric acid, in this test, to sulfuric acid, which will give a precipitate of barium sulfate upon the addition of barium chloride, T.S. Furthermore, if sulfur is present in the phosphorus or in the material from which the phosphorus is prepared, it will be oxidized along with the

$\text{Ꞥ}(SH)_5$ Pentathio-hydroxide	$\text{Ꞥ}S(SH)_3$ Monosulfide-trithio-hydroxide (Orthothio-ic Acid)	$\text{Ꞥ}S_2SH$ Disulfide-monothio-hydroxide (Metathio-ic Acid)	Ꞥ_2S_5 Pentasulfide (Thio-ic Acid Sulfanhydride)
$N(SH)_5$........	$NS(SH)_3$ Orthothionitric acid	NS_2SH Metathionitric acid	N_2S_5 Nitrogen pentasulfide
$P(SH)_5$........	$PS(SH)_3$ Orthothiophosphoric acid	PS_2SH Metathiophosphoric acid	P_2S_5 Phosphorus pentasulfide
$As(SH)_5$........	$AsS(SH)_3$ Orthothio-arsenic acid	AsS_2SH Metathio-arsenic acid	As_2S_5 Arsenic pentasulfide
$Sb(SH)_5$........	$SbS(SH)_3$ Orthothio-antimonic acid	SbS_2SH Metathio-antimonic acid	Sb_2S_5 Antimony pentasulfide
$Bi(SH)_5$........	$BiS(SH)_3$ Orthothiobismuthic acid	BiS_2SH Metathiobismuthic acid	Bi_2S_5 Bismuth pentasulfide

$N(SH)_3$ Trithiohydroxide (Orthothio-ous Acid)	$NS \cdot SH$ Monosulfide-monothiohydroxide (Metathio-ous Acid)	N_2S_3 Trisulfide (Thio-ous Acid Sulfanhydride)
$N(SH)_3$ .... Orthothionitrous acid	$NS \cdot SH$ Metathionitrous acid	N_2S_3 Nitrogen trisulfide
$P(SH)_3$ .... Orthothiophosphorous acid	$PS \cdot SH$ Metathiophosphorous acid	P_2S_3 Phosphorus trisulfide
$As(SH)_3$ .... Orthothio-arsenous acid	$AsS \cdot SH$ Metathio-arsenous acid	As_2S_3 Arsenic trisulfide
$Sb(SH)_3$ .... Orthothio-antimonous acid	$SbS \cdot SH$ Metathio-antimonous acid	Sb_2S_3 Antimony trisulfide
$Bi(SH)_3$ .... Orthothiobismuthous acid	$BiS \cdot SH$ Metathiobismuthous acid	Bi_2S_3 Bismuth trisulfide

phosphorus in the manufacture of phosphoric acid. The N.F. accordingly contains a test for sulfate as impurity in Phosphoric Acid.[45]

Arsenic occurs in nature more frequently as the sulfide than in any other form, hence it is to be expected that sulfides of arsenic, usually the trisulfide, may be found in both arsenic and sulfur and in the compounds made from them. Accordingly, there is a test for arsenic as impurity in all three of the official forms of sulfur. Likewise, the U.S.P. and N.F. include tests for arsenic as impurity in the compounds made from sulfur, e.g., sulfuric acid and its salts.

Sulfides of antimony and bismuth, chiefly the trisulfides known as stibnite and bismuth glance, respectively, are of natural occurrence.

Just as the oxides of the elements of group V are the anhydrides of the hydroxides or oxyacids, so may the sulfides be regarded as the sulfanhydrides of the thiohydroxides or thio acids and they have properties in common. Thus arsenic trisulfide, like the trioxide, is insoluble in water but soluble on long heating in hydrochloric acid and soluble in alkali hydroxide, alkali carbonate and alkali sulfide solutions. The hydration of arsenic trioxide and the sulfhydration of arsenic trisulfide may be shown in analogous reactions:

$$As_2O_3 + H_2O \rightarrow \underset{\text{Meta-arsenous Acid}}{2AsO \cdot OH} \xrightarrow{+2H_2O} \underset{\text{Ortho-arsenous Acid}}{2As(OH)_3}$$

$$As_2S_3 + H_2S \rightarrow \underset{\text{Metathio-arsenous Acid}}{2AsS \cdot SH} \xrightarrow{+2H_2S} \underset{\text{Orthothio-arsenous Acid}}{2As(SH)_3}$$

Likewise, the action of hydrochloric acid is as follows.

$$As_2O_3 + 6HCl \rightarrow 2AsCl_3 + 3H_2O$$

$$As_2S_3 + 6HCl \rightarrow 2AsCl_3 + 3H_2S$$

In alkali sulfide solutions, such as ammonium sulfide, T.S., arsenic trisulfide dissolves, with the formation of the corresponding ammonium salts of thio-arsenous acid, while in ammonium polysulfide, T.S., which

$$As_2S_3 + (NH_4)_2S \rightarrow \underset{\text{Ammonium Metathio-arsenite}}{2AsS(SNH_4)} \xrightarrow{+2(NH_4)_2S} \underset{\text{Tri-ammonium Orthothio-arsenite}}{2As(SNH_4)_3}$$

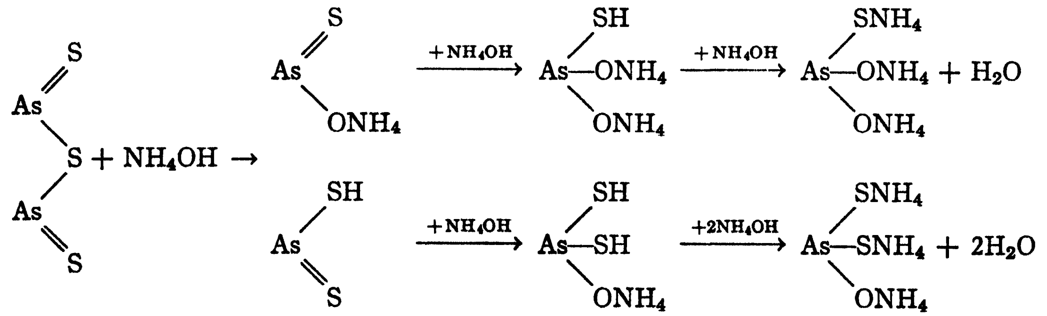
contains additional free sulfur in solution, arsenic trisulfide dissolves and is probably oxidized at the same time to the salt of the corresponding thio-arsenic acid:

$$As_2S_3 + 3(NH_4)_2S + 2S \rightarrow \underset{\text{Tri-ammonium Orthothio-arsenate}}{2AsS(SNH_4)_3}$$

The action of alkali hydroxide or alkali carbonate solutions on arsenic trisulfide is analogous to their action on the trioxide, although in this case, the analogy appears a bit more involved. Thus, whereas arsenic trioxide is dissolved by alkali carbonate, with the formation of the corresponding metallic salts of meta- and ortho-arsenous acids, as exemplified in the preparation of U.S.P. Potassium Arsenite Solution (p. 181); arsenic trisulfide is dissolved by the same reagent, with the formation of a mixture of the corresponding salts of meta- and ortho-arsenous acids and of meta- and orthothio-arsenous acids. An example of this is furnished in the preparation of N.F. Washed Sulfur.[46] As mentioned previously, Sublimed Sulfur may be contaminated with arsenic in the form of the trisulfide. In making Washed Sulfur, the Sublimed Sulfur is sieved, mixed with diluted ammonia, then set aside for three days with occasional agitation before being strained and washed free from alkali. During this period of contact, any arsenic trisulfide present in the sulfur reacts with the ammonia to form soluble ammonium salts of arsenous and thio-arsenous acids. The reaction is usually written as follows:

$$As_2S_3 + 6NH_4OH \rightarrow 3H_2O + \underset{\text{Tri-ammonium Ortho-arsenite}}{As(ONH_4)_3} + \underset{\text{Tri-ammonium Orthothio-arsenite}}{As(SNH_4)_3}$$

However, the above reaction probably does not give the entire picture of what happens; it can be explained more clearly by structural reactions in steps, as follows:



Whether the reaction mixture contains only the final products of tri-ammonium ortho-arsenite and tri-ammonium orthothio-arsenite, as shown in the empirical equation, or whether it contains the mixed salts, as shown in the structural equation, is a matter of speculation and is immaterial for purposes of explanation. The important point is that the reaction products, i.e., the ammonium salts of the acids shown above, are water-soluble and, upon straining the mixture at the end of three days and repeated washing of the undissolved sulfur with water, are removed, thus leaving the sulfur free from arsenic impurity.

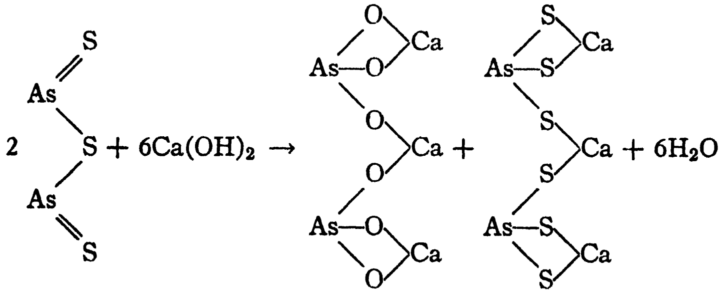
Analogous reactions taking place in the preparation of Precipitated Sulfur (p. 94) also serve to remove arsenic impurity. In this case the Sublimed Sulfur is boiled with calcium hydroxide and water until solution takes place, with the formation of soluble sulfides of calcium and calcium thiosulfate. At the same time, any arsenic trisulfide impurity is converted into soluble calcium ortho-arsenite and calcium orthothio-arsenate, the calcium orthothio-arsenite which

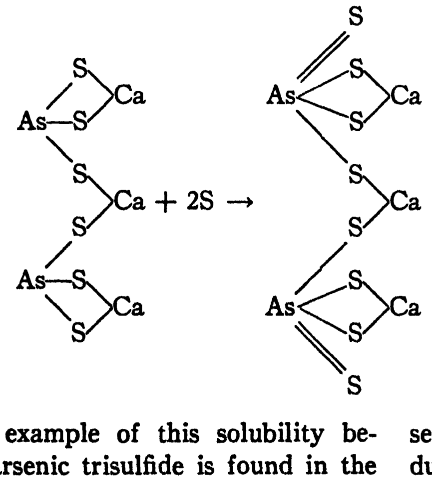
is first formed being oxidized, in the presence of the excess of sulfur to the pentavalent form:

$$2As_2S_3 + 6Ca(OH)_2 \rightarrow \underset{\text{Calcium Ortho-arsenite}}{As_2(O_2Ca)_3} + \underset{\text{Calcium Ortho-thio-arsenite}}{As_2(S_2Ca)_3} + 6H_2O$$

$$As_2(S_2Ca)_3 + 2S \rightarrow \underset{\text{Calcium Ortho-thio-arsenate}}{As_2S_2(S_2Ca)_3}$$

Again, this is more clearly shown by writing the reactions in a partially structural way:





Another example of this solubility behavior of arsenic trisulfide is found in the procedure used by the U.S.P. and N.F. to prepare a sample of one of the official forms of sulfur for the arsenic test itself.[47] The arsenic trisulfide impurity, if present, is converted into soluble ammonium salts of ortho-arsenous and orthothio-arsenous acids, as shown above, by digesting a sample of the sulfur with ammonia water and is removed from the remaining insoluble sulfur by filtration. Evaporation of the filtrate in the presence of nitric acid not only liberates the free acids from the ammonium salts:

$$2As(ONH_4)_3 + 6HNO_3 \rightarrow 6NH_4NO_3 + [2As(OH)_3] \rightarrow H_2O + As_2O_3$$

$$2As(SNH_4)_3 + 6HNO_3 \rightarrow 6NH_4NO_3 + [2As(SH)_3] \rightarrow H_2S + As_2S_3$$

but also oxidizes the arsenic trisulfide, which has been reprecipitated from the filtrate, into arsenic trioxide and sulfur dioxide. The latter escapes as a gas and leaves only arsenic trioxide, free from sulfur, in the residue, which is then submitted to the arsenic test.

The significance of this property of thioarsenite and thio-arsenate salts to be decomposed by acids with the precipitation of arsenic trisulfide and pentasulfide has also been emphasized in the preparation of Precipitated Sulfur (p. 94) and attention has been called to the possibility of recontami-

nating this product with arsenic if the directions are not followed carefully.

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12

Elements of Group IV

ELEMENTS

The elements of group IV fall into two classifications, namely, the carbon subgroup and the titanium subgroup. The carbon subgroup includes carbon, silicon, germanium, tin and lead, while the titanium subgroup consists of titanium, zirconium, cerium, hafnium and thorium. All of the elements can have a maximum positive valence of 4. Germanium, lead and tin readily lose 2 valence electrons; therefore, they commonly show an electropositive valence of 2. This tendency is much greater than it is in the case of carbon and silicon, which seldom exist in the bivalent state. Because they are transition elements (p. 202), the members of the titanium subgroup characteristically show a valence of +3. Therefore, when they are present in compounds in the tetravalent state, they are powerful oxidizing agents, and in the trivalent state they are good reducing agents. The +2 compounds of many of the transition elements are such strong reducing agents that hydrogen is released from their aqueous solutions.

Carbon and silicon are unusual in that numerous atoms of either element can join with like atoms to form long chains. This results from the sharing of valence bonds (covalence) between atoms rather than from the conventional type of electrovalence bonds.

Only carbon and silicon are nonmetals, the remaining elements in the group being metallic; however, the hydroxides of germanium, tin and lead are amphoteric. The elements of this group offer numerous illustrations of allotropism.

Germanium, zirconium and hafnium have no pharmaceutical application at present; therefore, they will not be included in the following discussion. However, they will be included in tabulations of physical properties of the elements in the group, so as to provide a more or less complete picture.

History of the Elements of the Carbon Subgroup. Carbon is one of those substances which has been, in either the free or the combined form, so intimately associated with the daily life of man, ever since his existence on the earth began, that the discovery of the element can be associated with neither time nor personality. It suffices to say that geologic studies of the earth's crust prove conclusively that carbon compounds have existed for millions of years. In her résumé on the discovery of the elements, Weeks[1] states, "Carbon in the form of charcoal and soot must certainly have been known even to prehistoric races, and in Pliny's time the former was made, much as it is today, by heating wood in a pyramid covered with clay to exclude the air." *

Compounds of silicon, such as sand and the clays, were fashioned into glass and pottery by the earliest civilizations. Free sili-

* Weeks, E.: Discovery of the Elements, Easton, Pa., Mack Printing Co., 1939, p. 7.

con, however, was isolated in 1824 by Berzelius, after unsuccessful attempts had been made by prominent investigators including Sir Humphry Davy, Gay-Lussac and Thenard.

Both tin and lead, like carbon and silicon, were mentioned previously among the elements known to the ancient world. Alloys of tin and copper were in use thirty centuries before the birth of Christ. This was possible primarily due to the fact that the ores of both metals were easily reduced by fire. The similarity between tin and lead necessitated distinguishing between them at an early date. During the first century A.D., tin was designated *plumbum album* and lead was called *plumbum nigrum*.[2] The Romans used tin and lead extensively in their aqueduct systems and in providing a protective coating for copper utensils.

History of the Elements of the Titanium Subgroup. The principle of electron exchange among elements which enter into chemical combination has been described briefly (p. 15). In the formation of the stable octet, only the electrons in the outer energy levels were involved, insofar as the illustrations given are concerned. Certain of the elements, however, may lose electrons from *two* main energy levels; these are called transition elements. The members of the titanium subgroup, Ti, Zr, Ce, Hf and Th, all are transition elements.

Titanium, named after the Titans of mythology, is unusual in several respects. It was discovered by an English clergyman, Reverend William Gregor, who observed in his parish an exceptionally interesting black sand with magnetic properties. In 1791, he published a record on his analysis of menachanite, the sandy ore, but since he did not succeed in isolating the new metal whose presence he suspected, his work drew little attention and was quickly forgotten. Klaproth, the famous chemist and pharmacist who a few years earlier had discovered the occurrence of uranium in pitchblende, took up the examination of the magnetic sand, and from it he isolated titanium.[3]

The isolation of cerium brought together some of the most famous names and minds in chemistry. Scheele examined the ore cerite in a search for tungsten, but reported that the ore contained no new metals. Berzelius and Hisinger (one of Sweden's most famous mineralogists), prodding the same source, but for yttria, encountered cerium, and their announcement was made simultaneously with that of Klaproth. The element was named for the planet Ceres, which had been discovered just prior to that time.[4]

Thorium was discovered by Berzelius in 1829. The metal attracted some attention because of its high specific gravity, but it stimulated little interest because of the great difficulty in isolating it. In 1898, Mme. Curie and G. C. Schmidt, working independently, observed that thorium is radioactive. Extended research showed thorium to be the parent substance of a series of radioactive elements.[5]

Occurrence. Carbon occurs extensively in the plant, animal and mineral kingdoms. In the mineral kingdom, it can be found in the free state as coal, which has almost a universal distribution. The other free forms are more localized in their distribution. Graphite is obtained in large quantities from mines located on the islands of Ceylon and Madagascar. Smaller deposits are located in North America and on the European continent. Diamonds are obtained in the largest quantities from Africa, though scattered stones have at one time or another been found in almost every country. Minerals containing carbon in the combined form are the insoluble metallic carbonates, such as calcium carbonate, chalk,[6] limestone, marble, calcite, dolomite, magnesium carbonate and zinc carbonate. Other metals, too numerous to mention, also occur in lesser quantities as the carbonates. The carbonates of calcium and magnesium, in general, have an universal distribution; the highly crystal-

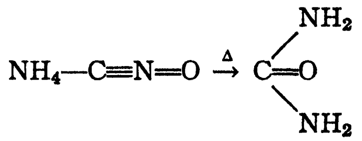
line forms, like marble and calcite, are localized in their occurrence.

In the plant kingdom, carbon, in the combined form peculiar to organic chemicals, constitutes a major portion of the tissues, ranging from cellulose, which makes up the cell walls and the plant skeleton, to the protoplasm of the cells themselves. In the production of food by the photosynthetic process, plants take into their tissues water and carbon dioxide (a waste product of the animal kingdom), which in the presence of chlorophyll and light are converted into sugars and other intermediate metabolites. These are further elaborated within the plant to provide for the essentials of the plant's living processes.

Carbon in organic combination likewise constitutes a major portion of the tissues of the animal body, while calcium as calcium carbonate makes up part of the skeletal structure; calcium phosphate also is present in bones to lend rigidity. It has been mentioned that the carbon dioxide, which is a waste product of animal metabolism and therefore exhaled into the air, is utilized by the plant as a raw material in the production of food. The plant, on the other hand, eliminates oxygen as a by-product of its metabolism, and oxygen of course is essential for all members of the animal kingdom. It would appear, then, that in this carbon dioxide-oxygen cycle, means of self-perpetuation in the two living kingdoms has been provided.

Less than 125 years ago, chemists were accustomed to draw a very fine line of distinction between the substances derived from the living kingdoms and from the nonliving or mineral kingdom. One of the most famous of the early texts in chemistry, Lemery's *Cours de Chymie*, published in 1675 (extended through thirteen editions and translated into five other languages), treated the subject on the basis of the three kingdoms, plant, animal and mineral. In 1812, Berzelius introduced the idea of a vital force. That is to say that the chemical substances produced in the living kingdoms could not have been produced in the absence of life itself. Extensive investigations were being conducted at that time in the field of plant chemistry. Scheele was especially successful in isolating and characterizing acids from plants. This was literally on the eve of Sertürner's isolation of morphine from opium, a discovery which opened upon a most fruitful era concerned with the examination of hundreds of species of plants for the purpose of isolating therapeutically active ingredients. In 1828, Wöhler, while attempting to prepare ammonium cyanate by heating together ammonium sulfate and potassium cyanate, obtained urea instead. Urea was known to exist in the urine of animals and therefore it was regarded a substance obtainable from the animal kingdom exclusively.

$$2K{-}C{\equiv}N{=}O + (NH_4)_2SO_4 \rightarrow 2NH_4{-}C{\equiv}N{=}O + K_2SO_4$$



Ammonium Cyanate   Urea

Wöhler's work showed that it was possible to produce artificially, or synthetically, those substances for which the vitalistic force previously had been deemed necessary. A few years later, Bergmann, of phlogiston fame, suggested the two subdivisions for all chemicals, namely, inorganic and organic. Bergmann, however, did not maintain the need for a living force as a basis of differentiation.

Kekulé, a pioneer in the development of structural chemistry, defined organic chemistry as the chemistry of the carbon compounds. This automatically left all noncarbon compounds to inorganic chemistry. To some, this sharp division has never seemed practical, perhaps because it definitely

placed all of the carbonates and bicarbonates in the organic category. The opposition is understandable for several reasons. Most of the metallic carbonates occur in nature as hard, rocky formations, and this indeed is typical of the inorganic or mineral kingdom. Truly, the carbonate radical has inherent properties and therefore undergoes specific reactions, but they are few in number. So, from a broad point of view, the most important ion with respect to the properties of a given metallic carbonate is the metallic or positive ion. It seems quite logical then that the carbonates be given extensive consideration by inorganic chemists and very minor consideration by organic chemists. The problem seems to have been solved partially by arbitrarily assigning compounds containing one carbon atom to the inorganic field and those containing two or more carbon atoms to the organic field. There are notable exceptions, of course, such as formates, cyanides and isocyanides, cyanates and isocyanates, etc., but it seems to have settled the question of what to do with the carbonates.

It never will be possible to differentiate sharply between the inorganic and the organic compounds. Fossil limestone and chalk indicate their origin from the shells of crustaceans. In some cases, the animals aggregated during life, as do the corals. In other cases, masses of invertebrates were buried lightly by the upheaval of the floor of the sea; in the case of crustaceans this gave rise to chalk, marine limestone and other amorphous forms of calcium carbonate. In still other cases, masses of marine animal life were overlaid by veritable mountains of dirt and rock and water. The tremendous pressure which developed at the bottom of the pile presumably was accompanied by temperatures sufficiently high to fuse the calcium carbonate skeletons into molten masses which then cooled very slowly, supposedly giving rise to marble and iceland spar, the two most highly crystalline forms of calcium carbonate.

Even today, mineral deposits of calcium carbonate are being formed partially from chemicals which find their origin in the animal kingdom and in the plant kingdom. The fermentive decomposition of organic matter pours vast amounts of carbon dioxide into the atmosphere. Every living animal contributes its share of carbon dioxide throughout its lifespan. Though the gas is not especially soluble in water, falling rain carries the carbon dioxide into the soil, where it possibly comes into contact with solutions of metallic salts of one kind or another. Frequently, insoluble carbonates or poorly soluble bicarbonates are formed, and a mineral deposit is in the process of formation. This principle is illustrated by the growth of stalactites and stalagmites in numerous subterranean chambers. Animals, plants and minerals are intimately related and there is no possibility of divorcing them from one another.

Silicon, in the form of its compounds, constitutes about 25 per cent of the earth's crust; the element is never found in the free state, because of its activity. The best source of silicon is its dioxide (SiO_2), which is found in mountainous regions as quartz crystals and nearly everywhere as sand. Silicon dioxide is officially represented by Purified Siliceous Earth.[7] In addition, there are numerous clays, metallic compounds of silicon, which have become economically important because of their diversified properties and uses. Talcum[8] [$H_2Mg_3(SiO_3)_4$], Kaolin[9] [$H_2Al_2(SiO_4)_2$] and Bentonite,[10] a native hydrated aluminum silicate, and Pumice,[11] are native silicates of pharmaceutical importance. The zeolites, $NaAl(SiO_3)_2 \cdot H_2O$, have gained prominence in the purification of water on the ion exchange basis.

Tin rarely occurs as the element. Its most important ore is cassiterite or tinstone, which contains SnO_2. The principal deposits are located in the Malay States, the Dutch East Indies and Bolivia. The tin mines of England have been worked, so far as re-

corded history reveals, since the early years of the Roman Empire.

Lead occasionally is found free in nature. Its principal ore is galena, PbS, which is widely distributed throughout North America and Australia. Missouri, Utah and Idaho lead in its domestic production.

Titanium compounds are abundant in the earth's crust. Its most common ores are ilmenite, $FeTiO_3$; ritule, TiO_2, and arizonite, $Fe_2O_3 \cdot 3TiO_2$. Titanium dioxide is official in the N.F.[12]

The remaining elements of the titanium subgroup are not abundant in nature. In general, these minerals are complex phosphates and silicates in which a number of the rare earth elements are represented. There are 14 of these elements, all occurring together in such minerals as gadolinite, found in Sweden, and monazite, in North Carolina.

Thorium, while not plentiful, is obtained in fair quantities from its ores, thorite and orangite, which contain the silicate $ThSiO_4$, and thorianite, which contains the oxide ThO_2.

Methods of Preparation and Isolation. Because of the great diversity of the ores or the raw materials from which the elements of this group are obtained, it is difficult, if not impossible, to designate a general method for the preparation or isolation of all of the elements. The one method which is applicable to all, with the exception of carbon itself, is the reduction of the oxide or dioxide with carbon. Thus,

$$SiO_2 + 2C \rightarrow Si + 2CO$$

$$SnO + C \rightarrow Sn + CO$$

$$TiO_2 + 2C \rightarrow Ti + 2CO$$

The reduction of oxides with carbon is an important reaction in metallurgical processes because the reaction is inexpensive and easy to conduct. It is essential, however, that sufficient carbon be present to insure the formation of carbon monoxide (which is in itself a reducing agent) and thereby guard against incomplete reduction of the oxides.

The reduction of the compound halides is applicable in certain cases, e.g.:

$$K_2SiCl_6 + 4K \rightarrow Si + 6KCl$$

$$K_2TiF_6 + 4K \rightarrow Ti + 6KF$$

$$K_2ThF_6 + 4K \rightarrow Th + 6KF$$

The commercial production of most of these elements is accomplished only by the application of specialized procedures.

Amorphous carbon generally is prepared by the destructive distillation of wood (wood charcoal), coal (coke) or bones (animal charcoal). The latter must be extracted with hydrochloric acid to free it of calcium carbonate and calcium phosphate. Coke, of course, is used extensively in industry and as a fuel, but it has no value as a laboratory or medicinal reagent. The charcoal or carbon is generally activated by heating it in retorts at high temperatures, in the presence of steam and carbon dioxide, to increase its adsorptive powers.

The dehalogenation of silicon halides is satisfactory for small scale operations, but commercially the element is best produced by reducing its dioxide with carbon, magnesium or aluminum. The following equations illustrate specific reactions:

(1) $SiF_4 + 4Na \rightarrow Si + 4NaF$

(2) $SiO_2 + 2Mg \rightarrow Si + 2MgO$

$2Mg + Si \rightarrow SiMg_2$

(3) $3SiO_2 + 4Al \rightarrow 3Si + 2Al_2O_3$

In the second reaction, the magnesium silicide is decomposed and the magnesium oxide is separated from silicon by means of dilute hydrochloric acid. Aluminum does not form a silicide; however, the silicon dissolves in the molten aluminum and the two metals are separated by the action of dilute hydrochloric acid.

As illustrated in the general reaction, tin is produced by reducing the dioxide with carbon; however, this reaction can be applied economically only after the ore has been concentrated by the floatation process.

Lead occurs most extensively as the sulfide. This ore likewise is concentrated by floatation before the roasting and reduction processes are undertaken.

$$4PbS + 7O_2 \rightarrow 2PbO + 2PbSO_4 + 2SO_2$$

$$PbSO_4 + PbS \rightarrow 2Pb + 2SO_2$$

$$PbO + C \rightarrow Pb + CO$$

Commercially, titanium is prepared by the thermite process. Other methods include the reduction of the dioxide and the dehalogenation of the double halides.

Cerium most generally is prepared by the electrolysis of ceric chloride

$$CeCl_4 \xrightarrow[\text{elect.}]{} Ce + 2Cl_2$$

Thorium is prepared primarily by the dehalogenation of potassium fluorothorate.

Physical Properties.

TABLE 31. PROPERTIES OF THE ELEMENTS OF THE CARBON SUBGROUP

	CARBON	SILICON	GERMANIUM	TIN	LEAD
Symbol	C	Si	Ge	Sn	Pb
Atomic weight	12.01	28.06	72.60	118.70	207.21
Isotopes	12, 13, 14	28, 29, 30	72, 73, 74, 75, 76, 77, 71, 70	118, 119, 120, 121, 122, 124, 117, 116, 115, 114, 113, 112	207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 206, 205, 204, 203, 202, 201
Atomic number	6	14	32	50	82
Density	Diamond 3.5 Graphite 2.25	Cryst. 2.48 Amorph. 2.35	5.36	α 5.75 β 7.28 γ 6.52	11.34
Melting point (°C.)	Sublimes 3,500	1,420	958	232	327

Elementary carbon resembles the other solid nonmetals in that it exists in a variety of allotropic forms. The so-called amorphous carbon actually is microcrystalline. It is represented by lampblack or soot, wood charcoal, animal charcoal, coal and coke, all of which contain varying amounts of impurity, as is demonstrated by the residue or ash remaining after combustion. The physical properties of carbon are closely related to the state of subdivision. It varies from a soft, light powder (Activated Charcoal U.S.P. and Purified Animal Charcoal N.F.) to the hard, brittle mass represented by coconut shell charcoal and coke. Activated charcoals (Norite and Darco) are microscopic masses with a high degree of porosity. This enables them to adsorb gases and solids, including pigments, alkaloids and other organic substances.

Amorphous carbon is black in color, and all forms of carbon are odorless and insoluble in any of the common solvents. The amorphous varieties and graphite will dissolve, however, in molten metals, especially iron.

Though it is macroscopically crystalline, graphite resembles amorphous carbon more closely than it resembles diamond. It is grayish-black in color and its soft, flaky crystals belong to the hexagonal system. It is a fair conductor of heat and electricity

and, like diamond, it is highly resistant to oxidation.

When pure, diamond is a colorless, highly crystalline form of carbon and it is characterized by extreme hardness. It has the highest density (3.5) of any known form of carbon and it is a good conductor of electricity. Because of its unparalleled hardness and high index of refraction, it is universally accepted as a precious stone.

Like carbon, the element silicon exists in two modifications: the amorphous, which actually is microcrystalline, and the crystalline. The former is a brown powder, while the latter exists as dark-gray crystals. Carbon sublimes at about 3,500° C., while silicon melts at 1,420° C. The crystalline variety is a poor conductor of electricity; the amorphous form does not conduct at all. Neither form is soluble in common solvents.

In Table 31 three allotropic forms of tin are listed. Their names and the temperatures at which they change from one form to another are as follows:

$$\underset{(\alpha\text{ tin})}{\text{Cubic Tin}} \xrightleftharpoons{18^\circ\text{ C.}} \underset{(\beta\text{ tin})}{\text{Tetragonal Tin}} \xrightleftharpoons{161^\circ\text{ C.}} \underset{(\gamma\text{ tin})}{\text{Rhombic Tin}} \xrightleftharpoons{231.9^\circ\text{ C.}} \text{Liquid Tin}$$

Tetragonal tin (β tin) obviously is the form most commonly encountered since this form exists at the prevailing normal temperatures. Ordinarily, tin is a soft, white metal, but the rhombic form is brittle, and as the temperature is raised above the melting point, the metal begins to oxidize. At higher temperatures it burns to the dioxide.

Lead is a bluish-white, silvery metal which is readily malleable, soft and ductile. When a bright surface of this dense metal is exposed to moist air, it soon becomes covered with a deposit of the basic carbonate, which functions as a protective coating against further oxidation.

Chemical Properties. Carbon, in any form, shows little tendency to react at ordinary temperatures. With the increase in temperature, the activity of the element increases. When heated to 800° C. in an atmosphere of oxygen, diamond burns entirely to carbon dioxide. Graphite likewise burns, but leaves an ash of from 2 to 5 per cent. Oxidation in an acid medium ($KClO_3$ and

TABLE 32. PROPERTIES OF THE ELEMENTS OF THE TITANIUM SUBGROUP

	TITANIUM	ZIRCONIUM	CERIUM	HAFNIUM	THORIUM
Symbol	Ti	Zr	Ce	Hf	Th
Atomic weight	47.90	91.22	140.13	178.60	232.12
Isotopes	47, 48	90, 91, 92, 94, 96	140, 142	....	229, 230, 231, 232, 233, 234, 235, 236
Atomic number	22	40	58	72	90
Density	4.5	6.4	6, 9	13.2	11.3
Melting point (°C.)	1,800	1,900	640	1,700	1,845
Color of Salts					
+2 valence	Brown to black	Black	....	....	....
+3 valence	Violet	Brown to black	Colorless	....	....
+4 valence	Colorless to yellow	Colorless	Yellow-brown	Colorless	Colorless

H_2SO_4) is the means of purifying graphite; however, when treated with alkaline permanganate or when employed as the positive electrode in an electrolysis system using an alkaline electrolyte, graphite is oxidized to mellitic acid, $C_6(COOH)_6$. Amorphous carbon is easily ignited and it is readily attacked by strong oxidizing agents. Because of the large quantities of heat liberated when carbon is converted into its oxides, it and its combustible compounds are used as fuels.

$$2C + O_2 \xrightarrow{\Delta} 2CO + 53.36 \text{ Cal.}$$

$$C + O_2 \xrightarrow{\Delta} CO_2 + 94.38 \text{ Cal.}$$

The first reaction is extensively employed in metallurgy, where the heat of formation of carbon monoxide and the reducing properties of the monoxide facilitate the liberation of metals from their oxides.

At extremely high temperatures, carbon combines with metals and some nonmetals to form carbides. Calcium carbide, CaC_2; silicon carbide, SiC; boron carbide, B_4C_3, and aluminum carbide, Al_4C_3, serve as illustrations of metallic carbides. Most of these compounds hydrolyze readily, yielding methane. Calcium carbide is unusual in that it yields acetylene.

$$Al_4C_3 + 12HCl \rightarrow 4AlCl_3 + 3CH_4$$

$$CaC_2 + 2HCl \rightarrow CaCl_2 + C_2H_2$$

or

$$CaC_2 + 2H_2O \rightarrow Ca(OH)_2 + C_2H_2$$

Carbon disulfide illustrates the nonmetallic carbides. It is a highly inflammable, water-insoluble liquid which is colorless but possessed of a very strong odor. It is extremely volatile.

$$C + 2S + 22 \text{ Cal.} \rightarrow CS_2$$

Carbon does not react directly with the halogens. Its union with hydrogen is accomplished only under the influence of extreme heat and high pressure. The reaction product is a mixture of hydrocarbons (p. 210).

Perhaps the most unusual chemical property of carbon is its ability to combine with itself. This reaction, which is not a reaction involving elementary carbon but carbon compounds instead, is illustrated on p. 210.

Silicon, like carbon, is an active sharer of electrons and as such it enters into a wide variety of combinations with itself, with metals and with nonmetals. It is not attacked by acids and it does not oxidize readily. Caustic alkalies attack it vigorously, liberating hydrogen.

$$Si + 4KOH \rightarrow Si(OK)_4 + 2H_2$$

It reacts with halogens to form the silicon tetrahalides, which form complex acids and complex salts with hydrogen halides and alkali halides. For example:

$$SiCl_4 + 2HCl \rightarrow \underset{\text{Chlorosilicic Acid}}{H_2SiCl_6}$$

$$SiF_4 + 2KF \rightarrow \underset{\text{Potassium Fluosilicate}}{K_2SiF_6}$$

The tetrahalide further combines with the halogen to form the hexahalide, thus, SiF_6, or $SiF_4 \cdot F_2$, is a silicohexahalide used as an antibiotic and antifermentive. It also is used in the control of mildew. With certain metals, including lithium, calcium, magnesium, iron, cobalt, manganese and platinum, silicon forms specific compounds (silicides); these generally are powerful reducing agents.

Tin commonly exhibits valences of +2 and +4. Generally, it does not react readily with dilute acids, but with hot, dilute hydrochloric acid the following reaction results:

$$Sn + 2HCl \rightarrow SnCl_2 + H_2$$

$$SnCl_2 + HCl \rightarrow HSnCl_3 \text{ or } SnCl_2 \cdot HCl$$

With hot, concentrated hydrochloric acid the reaction is as follows:

$$Sn + 4HCl \rightarrow SnCl_4 + 2H_2$$

Hot, concentrated sulfuric acid reacts with tin, forming stannous sulfate:

$$Sn + \text{conc. } H_2SO_4 \xrightarrow{\Delta} SnSO_4 + H_2$$

Tin reacts vigorously with aqueous solutions of caustic alkalies.

$$Sn + 2KOH + H_2O \rightarrow K_2SnO_3 + 2H_2$$

The free element is very resistant to oxidation, and for this reason tin is employed as a protective coating on less resistant metallic surfaces, such as iron and copper. Because of the ease in oxidizing Sn^{++} to Sn^{++++}, stannous salts are excellent reducing agents. For example,

$$2HgCl_2 + SnCl_2 \rightarrow 2HgCl + SnCl_4$$
$$2HgCl + SnCl_2 \rightarrow 2Hg + SnCl_4$$

This reaction is used in the U.S.P.[13] to test for the presence of stannous ions. Both stannous and stannic halides form double salts with other halides.

$$SnCl_2 + 2KCl \rightarrow SnCl_2 \cdot 2KCl \quad \text{or} \quad K_2SnCl_4$$

$$SnCl_2 + 2NH_4Cl \rightarrow SnCl_2 \cdot 2NH_4Cl \quad \text{or} \quad (NH_4)_2SnCl_4$$

$$SnF_4 + 2KF \rightarrow K_2SnF_6$$

Tin reacts with the halogens, forming compounds of the general formulae SnX_2 and SnX_4. A basic salt results when a stannous halide, like stannous chloride, reacts with oxygen in the presence of water.

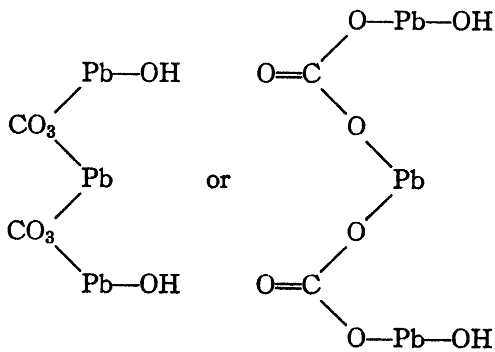
$$3SnCl_2 + H_2O + O \rightarrow 2\overset{Cl}{Sn}\text{—}OH + SnCl_4$$

Lead is similar to tin in that it too forms compounds in which it shows valences of +2 and +4. The lower valence state, which is the more stable one, is essentially basic, although with alkalies plumbous hydroxide, $Pb(OH)_2$, will form plumbites. That is to say it will act like an acid. The higher valence state is primarily acidic; however, it also is amphoteric, thus:

$$Pb(OH)_2 \xrightarrow{HCl} PbCl_2 \text{ (Plumbus Chloride)}$$
$$Pb(OH)_2 \xrightarrow{NaOH} NaPbO_2 \text{ (Sodium Metaplumbite)}$$

$$Pb(OH)_4 \xrightarrow{NaOH} Na_2PbO_3 \text{ (Sodium Metaplumbate)}$$
$$Pb(OH)_4 \xrightarrow{HCl} PbCl_4 \text{ (Plumbic Chloride)}$$

When heated in an atmosphere of oxygen, lead forms a red oxide, PbO, officially designated as Lead Monoxide.[14] In moist air, the oxidation of lead results in a basic carbonate, to which the following structural formula is assigned.



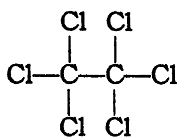
Lead is low in the electromotive series, being just above hydrogen, and consequently its reaction with dilute acids is very feeble. It is rapidly oxidized by nitric acid, however.

Titanium forms compounds in which it shows valences of +2, +3 and +4. The two lower states of oxidation are readily oxidized. Its compounds tend to form double salts, titanates, as was demonstrated in the cases of silicon and tin.

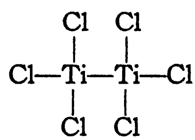
$$TiF_4 + 2HF \rightarrow H_2TiF_6$$

Other than its combinations with oxygen, titanium does not readily combine with other elements directly. The action of car-

bon and chlorine on titanium dioxide produces the tetrachloride, which, upon further chlorination, is converted to the hexachloride. In this compound, which is analogous to hexachlor ethane, there seems to be one illustration of a direct linkage between two atoms of titanium.



Hexachlor Ethane



Hexachlor Titane

The element burns readily in air. It decomposes hot water and dilute sulfuric and hydrochloric acids, liberating hydrogen.

Cerium forms two series of compounds, namely, the cerous (Ce^{+++}), which are colorless, and the ceric (Ce^{++++}), which are yellow to brown in color. Ceric salts are strong oxidizing agents and standard solutions of them [e.g., $Ce(SO_4)_2$] are used in some analytical procedures in place of permanganate and dichromate solutions. The following equation demonstrates the oxidation of a nitrite by ceric sulfate.

$$2Ce(SO_4)_2 + NaNO_2 + H_2O \rightarrow Ce_2(SO_4)_3 + NaNO_3 + H_2SO_4$$

Permanganate solutions have the disadvantage of being unstable, and when the dichromates are used, an outside indicator is required. The indicator used in cerimetric procedures is *o*-phenanthroline ferrous sulfate. In the oxidation reaction, the ferrous-ortho-phenanthroline complex, which is of an intense red color, is converted to the corresponding ferric complex, which is of a less intense blue color. Elementary cerium is fairly stable in the air, but it burns readily. It forms hydrides, CeH_2 and CeH_3, and a nitride, CeN.

Thorium on being heated in air is converted to ThO_2. The metal is poorly soluble in even concentrated acids and is insoluble in alkalies.

Uses. Carbon is the only member of group IV which has pharmaceutical uses as the element. It is recognized officially as Activated Charcoal U.S.P. and Purified Animal Charcoal N.F. They differ mainly in the selectivity of their adsorptive properties. Both are used internally to adsorb the gases and other reaction products of gastro-intestinal fermentation. Carbon can be used in the treatment of hyperacidity; however, the simultaneous adsorption of gastric enzymes may impair the digestive process. It has been recommended as an antidote in instances of poisoning from substances such as mercuric chloride, strychnine, morphine and the like. The technic of adsorption on carbon is applied industrially in decolorizing solutions of numerous compounds, such as sucrose and dextrose, and in the isolation of enzymes, hormones and antibiotics.

For the use of carbon isotopes, C^{13} and C^{14}, see pages 278-286.

HYDRIDES OF THE ELEMENTS

Introduction. The elements of the carbon subgroup form hydrides having the general formula ΘH_4 for the simplest compounds; however, the tendency to form them becomes less pronounced as the metallic properties of the respective elements increases. Hydrides of the titanium subgroup metals are thought to exist, but cerium hydride is the only one which is commonly listed in texts and reference books. Due to the high order of activity of the transition elements, hydrogen reduces them to their lowest state of valence; consequently, these hydrides have the general formula ΘH_2.

Hydrides of Carbon. Hydrides of carbon, or those compounds consisting only of carbon and hydrogen, are called hydrocarbons. The existence of these compounds is dependent upon the peculiar property of carbon, viz., atoms of carbon can become attached to one another in the form of chainlike configurations of various lengths and patterns. In these configurations, the carbon atoms are joined by the sharing of

valence bonds. The atoms are said to be covalent (p. 17). Since hydrocarbons form a nucleus for the classification of the many thousands of organic chemicals, the number of carbon hydrides is of necessity very large in itself.

Numerous hydrocarbons are obtained from natural sources, such as crude oil and coal, and many others are produced synthetically by a variety of reactions. These reactions, together with the study of the physical and chemical properties of the hydrocarbons, constitute a major portion of the field of organic chemistry. Some of the carbon hydrides, and very many of the compounds derived from them, are used in pharmaceutical practice.

Hydrides of Silicon. Silicon resembles carbon in that it too can form chainlike structures. However, the silicon hydrides, which also are known as silanes and silicanes, are by comparison very few in number. A systematic study of the "organic" chemistry of silicon has been begun, and it is entirely possible that in the future it too will be an extensive field. None of the hydrides of silicon has yet been shown to possess therapeutic value.

TABLE 33. SILICON HYDRIDES

FORMULA	NAMES	DESCRIPTION
SiH_4	Silane, silicane	Colorless gas
Si_2H_6	Disilicoethane, disilicane	Colorless gas
Si_3H_8	Trisilicopropane, trisilicane	Colorless liquid
Si_4H_{10}	Tetrasilicobutane	Colorless liquid

Hydrides of Germanium. In forming hydrides, germanium follows the pattern of carbon and silicon in part. The tetravalence of germanium predominates, but there is one exception, namely, germanium monohydride, which is unparalleled by either of the elements discussed before.

TABLE 34. GERMANIUM HYDRIDES

FORMULA	NAME	DESCRIPTION
GeH	Germanium monohydride	Brown powder
GeH_4	Germane	Colorless gas
Ge_2H_6	Digermane	Liquid
Ge_3H_8	Trigermane	Liquid

These compounds have neither natural occurrence nor pharmaceutical application.

Hydrides of Other Group IV Elements.

Stannane, (SnH_4) a colorless gas, is the only known hydride of tin.

Of the elements in the titanium subgroup, only cerium is known to form a hydride. Cerous hydride (CeH_2) is described as a dark blue, amorphous powder.

REFERENCES

1. Weeks, E.: Discovery of the Elements, Easton, Pa., Mack Printing Co., 1939, p. 7.
2. *Ibid.*, p. 6.
3. *Ibid.*, pp. 237-240.
4. *Ibid.*, p. 241.
5. *Ibid.*, p. 244.
6. See prepared chalk, U.S.P. XIII, p. 118.
7. U.S.P. XIII, p. 473.
8. *Ibid.*, p. 550.
9. N.F. VIII, p. 287.
10. U.S.P. XIII, p. 67.
11. N.F. VIII, p. 421.
12. *Ibid.*, p. 537.
13. U.S.P. XIII, p. 664.
14. N.F. VIII, p. 293.

13

Hydroxides (Oxyacids) of Group IV and Their Salts of Pharmaceutical Importance

TETRAHYDROXIDES
MONOXIDE-DIHYDROXIDES
THE META-IC ACIDS
SALTS OF THE META-IC ACIDS
THE "-IC" ACID ANHYDRIDES OR THE DIOXIDES
TRIHYDROXIDES
DIHYDROXIDES
MONOXIDES
OTHER HYDROXY ACIDS
OTHER OXIDES

Based on the patterns drawn previously, one would expect the elements of group IV to show electropositive valences of 4 and 2. In addition, the transition elements in the titanium subgroup commonly show an electropositive valence of 3. Therefore, considering the group as a whole, when these valence states are satisfied by the electronegative hydroxyl group, tetrahydroxides, trihydroxides and dihydroxides of the elements are derived. These, or their partial dehydration products, form the oxyacids of the elements of group IV.

TETRAHYDROXIDES

Using $\in$ as the symbol for the elements of the group, the tetrahydroxides and dehydration products derived are shown in tabular form on page 213.

Occurrence. The tetrahydroxides, or the ortho-ic acids, generally tend to lose water; consequently, none of them occurs naturally as such or in the form of salts.

Methods of Formation and Preparation.

I. Hydration of the Acid Anhydride.

$$CO_2 + H_2O \rightarrow CO(OH)_2 + H_2O \rightarrow C(OH)_4$$

$$CeO_2 + H_2O \rightarrow CeO(OH)_2 + H_2O \rightarrow Ce(OH)_4$$

This kind of reaction is of greater value theoretically than it is practically. The dioxides, acid anhydrides, do not have an affinity for water. If the reaction occurs at all, it does not do so readily. In fact, the reverse reaction is most prevalent.

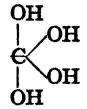
II. Action of Water on the Proper Salt.

$$\in X_4 + 4HOH \rightarrow \in(OH)_4 + 4HX$$
$$SiCl_4 + 4HOH \rightarrow Si(OH)_4 + 4HCl$$

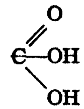
$$\in(SO_4)_2 + 2HOH \rightarrow \in(OH)_2SO_4 + H_2SO_4$$
$$\in(OH)_2SO_4 + 2HOH \rightarrow \in(OH)_4 + H_2SO_4$$
$$Ti(SO_4)_2 + 2HOH \rightarrow Ti(OH)_2SO_4 + H_2SO_4$$
$$Ti(OH)_2SO_4 + 2HOH \rightarrow Ti(OH)_4 + H_2SO_4$$

III. Treatment of an Appropriate Salt with an Hydroxide.

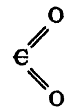
$$\in X_4 + 4NH_4OH \rightarrow C(OH)_4 + 4NH_4X$$
$$SiF_4 + 4NH_4OH \rightarrow Si(OH)_4 + 4NH_4F$$
$$TiCl_4 + 4NH_4OH \rightarrow Ti(OH)_4 + 4NH_4Cl$$
$$ThBr_4 + 4NH_4OH \rightarrow Th(OH)_4 + 4NH_4Br$$



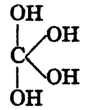
TETRAHYDROXIDE
ORTHO-IC ACID



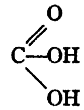
MONOXIDE, DIHYDROXIDE
META-IC ACID



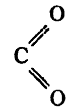
DIOXIDE
"-IC" ACID ANHYDRIDE



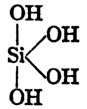
Orthocarbonic Acid



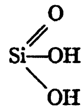
Metacarbonic Acid *



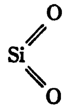
Carbonic Acid Anhydride *
(Carbon Dioxide)



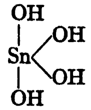
Orthosilicic Acid



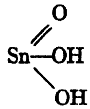
Metasilicic Acid *



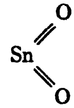
Silicic Acid Anhydride *
(Silicon Dioxide)



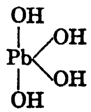
Orthostannic Acid



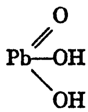
Metastannic Acid



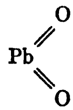
Stannic Acid Anhydride *
(Tin Dioxide)



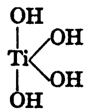
Orthoplumbic Acid



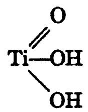
Metaplumbic Acid



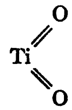
Plumbic Acid Anhydride *
(Lead Dioxide)



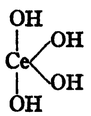
Orthotitanic Acid



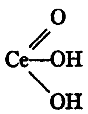
Metatitanic Acid



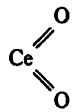
Titanic Acid Anhydride *
(Titanium Dioxide)



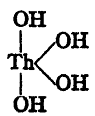
Orthoceric Acid *



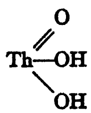
Metaceric Acid



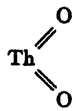
Ceric Acid Anhydride
(Cerium Dioxide)



Orthothoric Acid *



Metathoric Acid



Thoric Acid Anhydride
(Thorium Dioxide)

* Compounds that are of pharmaceutical importance and are official in the U.S.P. or the N.F., either as such or in the form of salts.

The alkali hydroxides cannot be used in these reactions because the acids formed would react with them to yield water-soluble salts.

IV. Action of a Caustic Alkali on the Element.

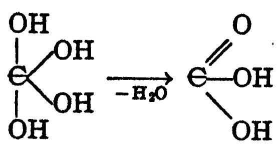
$$Si + 4KOH \rightarrow Si(OK)_4 + 2H_2$$

$$Si(OK)_4 + 4HCl \rightarrow Si(OH)_4 + 4KCl$$

This reaction is unusual for the elements of the carbon subgroup, but it is more common for the active metals of the titanium subgroup.

Properties. In those cases where the tetrahydroxide has been isolated and is known to exist [$Si(OH)_4$, $Ti(OH)_4$ and $Th(OH)_4$], it has separated from aqueous solution as a gelatinous mass, when freshly precipitated. In other instances, the passing existence of the ortho-ic acids can be supposed on the basis of salts derived from them and on the basis of the methods of preparing some of these salts. Thus, the existence of orthocarbonic and orthostannic acids is doubtful because, other than the halides (which are not prepared through the hydroxides), there are no known salts derivable from the tetrahydroxides. On the other hand, calcium orthoplumbate, Ca_2PbO_4, indicates the possible existence of orthoplumbic acid, which never has been isolated.

Thus, the outstanding reaction of the ortho-ic acids is their tendency to lose water in the formation of the corresponding meta-ic acid.



$$Si(OH)_4 \xrightarrow[-H_2O]{} SiO(OH)_2$$

As suggested earlier, this loss of water as soon as the tetrahydroxide is removed from the aqueous medium usually is spontaneous; however, in the case of titanium the abstraction of water is accomplished only in the presence of dehydrating agents.

$$Ti(OH)_4 \xrightarrow[H_2SO_4]{} TiO(OH)_2$$

The ortho-ic acids are amphoteric. In the presence of strong acids they react basically: e.g.,

$$\epsilon(OH)_4 + 4HX \rightarrow \epsilon X_4 + 4HOH$$

$$Si(OH)_4 + 4HF \rightarrow SiF_4 + 4HOH$$

$$Th(OH)_4 + 2H_2SO_4 \rightarrow Th(SO_4)_2 + 4HOH$$

$$Ce(OH)_4 + 2H_2SO_4 \rightarrow Ce(SO_4)_2 + 4HOH$$

$$Th(OH)_4 + 4HNO_3 \rightarrow Th(NO_3)_4 + 4HOH$$

The ortho-ate salts are formed when the ortho-ic acids react with strong alkalies.

$$\epsilon(OH)_4 + 4KOH \rightarrow \epsilon(OK)_4 + 4H_2O$$

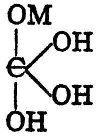
$$Si(OH)_4 + 4KOH \rightarrow Si(OK)_4 + 4H_2O$$

This reaction does not hold true for $Th(OH)_4$ or $Ti(OH)_4$.

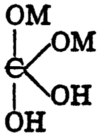
Pronounced instability among the tetrahydroxides is shown also by the fact that pyro acids of these elements are not known; neither are salts of pyro acids known. Ordinarily, the pyro acid results from the removal of a molecule of water between two molecules of an ortho acid with the aid of heat. When these tetrahydroxides are heated, they form the meta-ic acids. Silicic, stannic and titanic tetrahydroxides possibly form poly-acids, however, which are represented by the salts $Na_2Sn_4O_9$, $Na_2Ti_8O_7$, etc.

Salts of the Acids

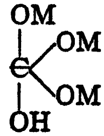
Since they are tetrabasic acids, one would expect four series of salts to be formed, namely,



I



II



III

IV

There are no known representatives of types I, II and III. Type IV is illustrated by tetrapotassium orthosilicate and dicalcium orthoplumbate (Ca_2PbO_4), neither of which is official. There are only two derivatives of the tetrahydroxides which are given official recognition. Thorium Nitrate, $Th(NO_3)_4$, U.S.P.[1] generally is used in qualitative tests for ferrous ferric cyanide and for fluorides. Therapeutically, it is employed as an astringent, and because of its radioactivity, it is sometimes applied externally in the treatment of malignant diseases. Ceric Sulfate, also listed among the U.S.P. reagents,[2] is used as an oxidizing agent in analytical procedures. (See p. 210; also see Menadione U.S.P.)

MONOXIDE-DIHYDROXIDES

The Meta-ic Acids

The monoxide-dihydroxides, or the meta-ic acids, can be regarded as dehydration products of the ortho-ic acids or as hydration products of the acid anhydrides (the dioxides). These acids and/or their salts are widely distributed in nature.

Occurrence. Whether carbon dioxide simply dissolves in water or combines with water to form metacarbonic acid is immaterial, because the aqueous solution reacts in the manner typical of meta-acids. Traces of the acid constantly are in the moist atmosphere, and even larger quantities permeate the soil. Natural salts of the acid include calcium carbonate, magnesium carbonate, etc.

Metasilicic acid does not occur as such, but common salts in the form of clays and various earths include calcium silicate, magnesium silicate and the aluminum complexes like $Na_2Al_2(SiO_4)_2$, etc. The silicates of the alkali metals are only slightly soluble in water, yet they do not occur naturally. Metastannic and metaplumbic acids are well represented by numerous salts; however, none of them occurs in nature, possibly due to their solubility in water or other types of activity.

Ilmenite, $FeTiO_3$, is the only naturally occurring representative of metatitanic acid. Other salts, including the potassium, calcium and magnesium titanates, are well-known. Neither metaceric nor metathoric acid is known to exist.

Methods of Formation and Preparation. Two methods for the formation of the meta-ic acids have already been suggested.

I. Dehydration of the Ortho-ic Acid.

$$\mathcal{E}(OH)_4 \xrightarrow[-H_2O]{} \mathcal{E}O(OH)_2$$

$$Ti(OH)_4 \xrightarrow[-H_2O]{} TiO(OH)_2$$

II. Hydration of the "-ic" Acid Anhydride.

$$\mathcal{E}O_2 + H_2O \rightarrow \mathcal{E}O(OH)_2$$

$$CO_2 + H_2O \rightarrow H_2CO_3$$

This hydration under the influence of an alkali is represented:

$$PbO_2 + 2KOH \rightarrow K_2PbO_3 + H_2O$$

Other methods of preparing them include:

III. Acidification of the Appropriate "-ate" Salt.

$$M_2\mathcal{E}O + 2HCl \rightarrow 2MCl + H_2\mathcal{E}O_3$$

$$Na_2SiO_3 + 2HCl \rightarrow 2NaCl + H_2SiO_3$$

This method is applied readily in preparing the corresponding acids of tin, lead and titanium.

IV. Oxidation of the Corresponding Ortho-ous Acid or Salt.

$$2\mathcal{E}(OH)_2 + O_2 \rightarrow 2\mathcal{E}O(OH)_2$$

$$2Sn(OH)_2 + O_2 \rightarrow 2SnO(OH)_2$$

This reaction is illustrative of the reducing powers of stannous compounds in general.

V. Oxidation of the Corresponding Metal by Alkali Hydroxides.

$$\mathcal{E} + 2MOH + H_2O \rightarrow \mathcal{E}O(OM)_2 + H_2O$$

$$Sn + 2KOH + H_2O \rightarrow K_2SnO_3 + H_2O$$

$$K_2SnO_3 + 2HCl \rightarrow H_2SnO_3 + 2KCl$$

Because they are readily oxidized, this reaction applies also to the metals of the titanium subgroup.

VI. Hydrolysis of the Tetrahalide.

$$SnCl_4 + 3H_2O \rightarrow H_2SnO_3 + 4HCl$$

Actually, this is a combination of two reactions:

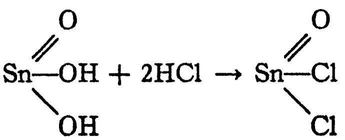
$$SnCl_4 + 4H_2O \rightarrow H_4SnO_4 + 4HCl$$

$$H_4SnO_4 \xrightarrow[-H_2O]{} H_2SnO_3$$

Properties. In this series, the meta-ic acids represent the most stable form of the acids of group IV. It is true that they may become hydrated to the tetroxide and they do dehydrate to the dioxide, yet most of the reactions of the elements of group IV in their tetravalent state take place through the meta-ic acids.

They have a pronounced tendency to be amphoteric. Thus, when stannic acid is treated on the one hand with a base and on the other hand with an acid, the following results are obtained:

$$2NaOH + H_2SnO_3 \rightarrow Na_2SnO_3 + 2H_2O$$



or

$$SnOCl_2 + 2H_2O$$

They react basically only when brought into contact with strong acids. The meta-ic acids of this group are very weak acids, and they do not form two series of salts simply because they contain two replaceable hydrogens. Consequently, the salts formed from the acids are the normal salts. Most remarkably, metacarbonic acid is the exception in this case, since it forms two series of salts, namely, the bicarbonates and the carbonates. This would lead one to believe that metacarbonic acid (weak as it is) is the strongest acid in this series; however, this is correct because carbon has the strongest nonmetallic tendencies of the elements in group IV.

Silicic acid is a colorless, gelatinous mass which has a high degree of porosity when deprived of all but 5 per cent of its water. This is used to advantage in adsorbing gases and water in air-conditioning devices. It also is an excellent filtering medium.

Two forms of metastannic acid are listed, but their identities are questionable. They are α-stannic acid, H_2SnO_3, and β-stannic acid, $H_{10}Sn_5O_{15}$. Both are described as gelatinous masses which are of a colloidal nature when suspended in water.

Salts of the Meta-ic Acids

As was mentioned previously, although the meta-ic acids are dibasic, they generally form a single series of salts, namely, the normal salts. Metacarbonic acid is unusual in this respect since it forms both the acid and the basic salts.

The bicarbonates can be prepared by either of the following reactions:

1. $M'OH + H_2CO_3 \rightarrow M'HCO_3 + HOH$
2. $M'_2CO_3 + H_2CO_3 \rightarrow 2M'HCO_3$

Though numerous metals form bicarbonates, only sodium bicarbonate ($NaHCO_3$) and potassium bicarbonate ($KHCO_3$) are given official recognition.[3] Though they are referred to as the acid salts, they are mildly alkaline in reaction. Sodium Bicarbonate U.S.P. is used extensively as an antacid and Potassium Bicarbonate is used primarily in carbonating Magnesium Citrate Solution.[4] This preparation contains an excess of citric acid, and in order to make the solution more palatable, it is carbonated by the acid decomposition of potassium bicarbonate.

$$H_3C_6H_5O_7 + KHCO_3 \rightarrow KH_2C_6H_5O_7 + HOH + CO_2$$

Both sodium and potassium bicarbonates are used extensively in buffer systems, and in this capacity they are normal constituents of blood serum. The bicarbonates are incompatible with all acids and with acid

salts. They can be used as antidotes for poisoning from noncorrosive acids.

Normal metallic carbonates are numerous. The normal carbonates of the alkali metals are more soluble in water than the corresponding bicarbonates, and their aqueous solutions are strongly alkaline. On the other hand, the carbonates of the alkaline earth metals are less soluble than the corresponding bicarbonates, and their aqueous solutions are neutral. The carbonates of the heavy metals and the noble metals are insoluble in water. Like the bicarbonates, the normal carbonates are incompatible with acids and with acid salts. This reaction is used in the U.S.P. test for carbonate and bicarbonate.[5] The carbonates of the alkali metals are not well suited for treating noncorrosive acid poisoning because their aqueous solutions are too strongly alkaline. The alkaline earth carbonates, especially $CaCO_3$ and $MgCO_3$, however, are well suited for this purpose. Generally, the normal carbonates are prepared by the action of carbonic acid on the appropriate alkali:

$$2M'(OH) + H_2CO_3 \rightarrow M'_2CO_3 + 2HOH$$

$$2KOH + H_2CO_3 \rightarrow K_2CO_3 + 2HOH$$

They can also be prepared by double decomposition reactions in which the carbonate separates as an insoluble precipitate.

$$CaCl_2 + Na_2CO_3 \rightarrow CaCO_3 + 2NaCl$$

Sodium carbonate, which is important in many industrial applications, can be prepared by both the LeBlanc and the Solvay processes. The former has been described in detail in connection with the preparation of hydrogen chloride (p. 41). In the Solvay process, brine is saturated with ammonia, causing the precipitation of the hydroxides of iron and magnesium. The clarified solution is treated with carbon dioxide, and the sodium bicaronate which forms is partially precipitated.

$$NH_4OH + CO_2 \rightarrow NH_4HCO_3$$

$$NaCl + NH_4HCO_3 \rightarrow NaHCO_3 + NH_4Cl$$

After being washed and dried, the product is heated to produce the normal carbonate.

$$2NaHCO_3 \xrightarrow{\Delta} Na_2CO_3 + CO_2 + H_2O$$

The Solvay process is very economical because the by-products can be put to further use. The carbon dioxide evolved in the decomposition of the bicarbonate is returned to the reaction chambers for the formation of more ammonium bicarbonate. The ammonium chloride can be decomposed into ammonia and calcium chloride according to the equation

$$2NH_4Cl + CaO \rightarrow 2NH_3 + CaCl_2 + H_2O$$

or it can be purified and then marketed as such. The ammonia produced is returned to the initial reaction chamber, and the calcium chloride is regarded a useful by-product. The lime used in decomposing ammonium chloride is obtained from the limestone which served as the original source of carbon dioxide.

Table 35 shows the official carbonates.

TABLE 35. OFFICIAL CARBONATES

NAME	FORMULA	USE
Lithium Carbonate N.F.	Li_2CO_3	No practical value
Monohydrated Sodium Carbonate U.S.P.	$Na_2CO_3 \cdot H_2O$	Reagent; water softening, alkaline wash
Potassium Carbonate U.S.P.	$K_2CO_3 \cdot 1\frac{1}{2}H_2O$	Same as above
Precipitated Calcium Carbonate U.S.P.	$CaCO_3$	Antacid
Prepared Chalk U.S.P.	$CaCO_3$	Antacid
Basic Lead Carbonate U.S.P.	$PbCO_3 \cdot Pb(OH)_2$	Reagent

In addition to those carbonates mentioned above, the U.S.P. recognizes Ammonium Carbonate, which is not a carbonate at all, but instead a mixture of ammonium

bicarbonate and ammonium carbamate. See page 159.

The so-called Ammonium Carbonate is a very unstable compound, being a ready source of ammonia (30 to 33 per cent), which it liberates slowly but spontaneously. Crystals of it commonly are colored and perfumed and sold as smelling salts. It serves as a general stimulant.

The conversion from bicarbonate to the carbonate and vice versa is readily effected, and extensive use is made of this relationship industrially and domestically. The universal distribution of calcium and magnesium carbonates was mentioned. Rainwater passing through the air dissolves carbon dioxide, thereby becoming a very dilute solution of metacarbonic acid. As this rainwater flows over the earth and trickles through the soil, it comes into contact with calcium or magnesium carbonate, or possibly both, with the following result:

$$CaCO_3 + H_2CO_3 \rightarrow Ca(HCO_3)_2$$
$$MgCO_3 + H_2CO_3 \rightarrow Mg(HCO_3)_2$$

The presence of traces of either of these bicarbonates lends temporary hardness to water. Temporary hardness is hardness which can be removed by both physical and chemical means. Permanent hardness, on the other hand, which results from the presence of the usual cations along with anions other than bicarbonates (SO_4^{--}, Cl^-, NO_3^-, etc.), may be softened only by chemical means.

Hardness, it should be pointed out, deals with the formation of insoluble soaps. Soaps usually (but not exclusively) are defined as the metallic salts of fatty acids. Those which are used as detergents must be soluble in water so that they can lower the surface tension of the water and thereby aid in the cleansing process. Therefore, when water contains metallic ions which form insoluble soaps, they are precipitated in the form of a curd. In this form, they do not affect the surface tension of water materially and the cleansing process is hindered instead of being facilitated.

Temporary hardness can be overcome by boiling water, thereby converting the soluble bicarbonates to insoluble carbonates, which are then precipitated.

$$Ca(HCO_3)_2 \xrightarrow{\Delta} CaCO_3 + HOH + CO_2$$

Or, it can be overcome by adding a weak alkali, as

$$Ca(HCO_3)_2 + Ca(OH)_2 \rightarrow 2CaCO_3 + 2H_2O$$

Permanent hardness is overcome by the addition of a soluble carbonate.

$$Mg^{++} + SO_4^{--} + Na_2CO_3 \rightarrow CaCO_3 + Na_2SO_4$$

Both kinds of hardness are currently overcome on a large scale basis through ion-exchange reactions. The active chemical reagents in these reactions are related to the natural zeolites or sodium aluminum silicate. As the hard water flows through a zeolite bed, the calcium and other cations which cause hardness displace the sodium from the zeolite.

$$Na_2Z\,^* + Ca^{++} \rightarrow CaZ + 2Na^+$$

When the original zeolite is exhausted, it can be regenerated.

$$CaZ + 2NaCl \rightarrow Na_2Z + CaCl_2$$

Metasilicic acid readily forms salts having the general formula $M_2{}^+SiO_3$, $M^{++}\cdot SiO_3$, $M_2{}^{+++}(SiO_3)_3$, etc. Solutions of these salts have a tendency to be of a colloidal nature. Sodium metasilicate, a compound of unknown identity generally indicated as Na_2SiO_3, formerly was used in preserving eggs. Eggs immersed in an aqueous solution of the compound become coated with a gelatinous film, thereby reducing the porosity of the shell.

Bentonite U.S.P. is defined as a native, hydrated aluminum silicate, presumably

* The symbol Z is used to illustrate the bivalent zeolite radical.

$Al_2(SiO_3)_3 \cdot XH_2O$. It is unusual in that when in contact with water, it swells to about 8 times its normal volume, forming a colloid. It is used as a suspending agent in Calamine Lotion U.S.P. and it has been recommended as a substitute for starch to aid in the disintegration of tablets.

Pumice, a strong abrasive formerly used in some dental creams, is described in the U.S.P. as a mixture of sodium and potassium aluminum silicates of volcanic origin.

Though the name is suggestive of a relationship, Magnesium Trisilicate U.S.P.[6] is not derived from metasilicic acid (see p. 221). The tin salts, both stannic and stannous, would of necessity be derived from metastannic and from orthostannous acids. The soluble compounds are toxic for all forms of living matter. Possibly because the therapeutic index (the ratio of the effective dose to the toxic dose) is low, compounds of tin have not been employed as medicinal agents. When applied locally, the salts are astringents and antiseptics.

Numerous lead salts are employed in pharmaceutical practice; however, most of them are derived from orthoplumbous acid instead of from metaplumbic acid. There are two exceptions, namely, Lead Peroxide U.S.P. (see p. 221) and Basic Lead Carbonate U.S.P. The latter is a mixed salt of both plumbic and plumbous lead, usually designated by the formula $Pb(CO_3)_2 \cdot Pb(OH)_2$. It is an insoluble white compound which forms when soluble lead salts are treated with a soluble carbonate in the presence of air and water.

$$4Pb(NO_3)_2 + 4Na_2CO_3 + O_2 + 2H_2O \rightarrow 2Pb(CO_3)_2 + 2Pb(OH)_2 + 8NaNO_3$$

It also is formed by the action of air and moisture on the free metal, thus providing a protective coating for the metal.

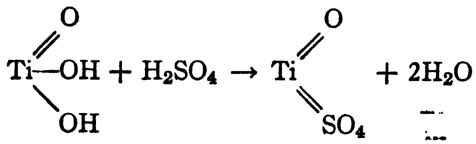
$$3Pb + 2O_2 + 2H_2O + 2CO_2 \rightarrow Pb(CO_3)_2 + 2Pb(OH)_2$$

The formation of the basic carbonate represents an incompatibility which exists between the lead salts of weak acids and atmospheric carbon dioxide.

$$3Pb(OCOCH_3)_2 + 4H_2O + 4CO_2 + O_2 \rightarrow 2Pb(CO_3)_2 + Pb(OH)_2 + 6CH_3COOH$$

The precipitate is soluble in dilute acetic acid. For this reason, solutions of lead acetate used as a reagent usually are rendered acidic with acetic acid.

Metatitanic acid, H_2TiO_3, forms salts of the type K_2TiO_3 and $CaTiO_3$. Solutions of these soluble titanates are hydrolyzed to $Ti(OH)_4$ by boiling. Being amphoteric, the monoxide dihydroxide reacts with strong acids like sulfuric acid:



None of the salts of metatitanic acid is used in pharmaceutical practice.

Metaceric (H_2CeO_3) and metathoric (H_2ThO_3) acids are not known to exist either as such or in the form of salts.

The "-ic" Acid Anhydrides or the Dioxides

The dioxides are the so-called "-ic" acid anhydrides of the elements of group IV. A number of them occur extensively in nature. Carbon dioxide results from the complete oxidation of organic compounds, and as such it is a waste product of animal metabolism. Carried by the hemaglobin of the blood stream, it is transported from the tissues, where it forms, to the lungs from which it is exhaled. Though excessive concentrations of carbon dioxide are toxic, extremely low concentrations in the blood stream are necessary for the proper functioning of the respiratory enzymes. Chemistry text books generally list the carbon dioxide content of the atmosphere as 0.3 per cent. The combustion of fuels produces huge quantities of carbon dioxide. The mil-

lions of internal combustion engines give off a mixture of carbon dioxide and monoxide in their exhaust gases because the fuel is burned in a limited quantity of oxygen. Eventually, the monoxide, which is highly toxic, is oxidized atmospherically to carbon dioxide; nevertheless, in large cities, among tall buildings and when motor vehicle traffic is heavy, symptoms of carbon monoxide poisoning are not uncommon. That simple part of the respiratory process which involves the inhalation of oxygen (air) and the exhalation of carbon dioxide (plus the nitrogen and other atmospheric gases not utilized by the body) represents one of the most spectacular illustrations of the diffusion of gases. The remainder of the respiratory process illustrates diffusion too, but of an extremely complex order.

Silicon dioxide is more abundant than carbon dioxide since, in both the free and combined forms, it constitutes a major part of the earth's crust. This has been described in detail under the occurrence of the element silicon (p. 204). The natural occurrence of the dioxides of the remaining elements of group IV has also been described.

Methods of Formation and Preparation.

I. Oxidation of the Element.

$$\text{Є} + O_2 \rightarrow \text{Є}O_2$$
$$C + O_2 \rightarrow CO_2$$
$$Si + O_2 \rightarrow SiO_2$$

etc.

The oxides of all of these elements can be formed in this way, and in fact, most of them form spontaneously. Carbon and silicon, however, must be burned in the oxygen atmosphere.

II. Oxidation (Burning) of the Hydrides of the Elements.

$$\text{Є}H_4 + 2O_2 \rightarrow \text{Є}O_2 + 2H_2O$$
$$CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O$$
$$SiH_4 + 2O_2 \rightarrow SiO_2 + 2H_2O$$
$$ThH_4 + 2O_2 \rightarrow ThO_2 + 2H_2O$$

etc.

Any of the many hydrides of carbon, silicon, etc., can be burned to the dioxides.

III. Oxidation of the Corresponding Monoxide.

$$2\text{Є}O + O_2 \rightarrow 2\text{Є}O_2$$
$$2CO + O_2 \rightarrow 2CO_2$$
$$2SnO + O_2 \rightarrow 2SnO_2$$
$$2PbO + O_2 \rightarrow 2PbO_2$$

IV. Dehydration of the Corresponding Meta-ic Acid.

$$H_2\text{Є}O_3 \rightarrow \text{Є}O_2 + H_2O$$

This reaction already has been profusely illustrated.

V. Treatment of an "-ate" Salt with an Acid and the Subsequent Dehydration of the Resulting "-ic" Acid.

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

There are special methods of preparation and handling for carbon dioxide because it is a gas. It can be liberated from metallic carbonates by heating.

$$M''CO \xrightarrow{\Delta} M''O + CO_2$$
$$CaCO_3 \xrightarrow{\Delta} CaO + CO_2$$
$$ZnCO_3 \xrightarrow{\Delta} ZnO + CO_2$$

etc.

Carbon dioxide can be obtained by liquefaction and subsequent fractional distillation of the air because it occurs in the atmosphere. Large quantities of the gas are obtained as a by-product of the fermentation industry.

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$

It is collected from the fermentation vats, compressed into a liquid and filled into tanks for distribution.

Properties and Uses. The dioxides readily are reduced by carbon to either the monoxide or the free element.

$$ЄO_2 + C \rightarrow Є + CO_2$$
$$CO_2 + C \rightarrow 2CO$$
$$SnO_2 + C \rightarrow Sn + CO_2$$
$$PbO_2 + C \rightarrow Pb + CO_2$$

This reaction is employed extensively in metallurgy.

Acids, usually concentrated, react with most of the dioxides, forming a variety of salts, depending upon the acid used and also upon the nature of the dioxide.

$$SiO_2 + 4HF \rightarrow SiF_4 + 2H_2O$$

$$SnO_2 + 4HCl \rightarrow SnCl_4 + 2H_2O$$
$$SnCl_4 + 3H_2O \rightarrow H_2SnO_3 + 4HCl$$

$$2PbO_2 + 2H_2SO_4 \rightarrow 2PbSO_4 + 2H_2O + O_2$$

$$PbO_2 + 4HCl \rightarrow PbCl_4 + 2H_2O$$
$$PbCl_4 \rightarrow PbCl_2 + Cl_2$$

$$ThO_2 + 2H_2SO_4 \rightarrow Th(SO_4)_2 + 2H_2O$$

Alkalies as a rule react with the dioxides, forming metallic salts of the meta-ic acids. Thorium dioxide does not react in this way.

$$CO_2 + NaOH \rightarrow NaHCO_3$$
$$CO_2 + 2NaOH \rightarrow Na_2CO_3 + H_2O$$
$$SiO_2 + 2NaOH \rightarrow Na_2SiO_3 + H_2O$$
$$SnO_2 + 2NaOH \rightarrow Na_2SnO_3 + H_2O$$
$$PbO_2 + 2NaOH \rightarrow Na_2PbO_3 + H_2O$$
$$TiO_2 + 2NaOH \rightarrow Na_2TiO_3 + H_2O$$

All of the dioxides are solids except carbon dioxide, which is a gas. Carbon dioxide is colorless and odorless. It dissolves in water to the extent of 90 volumes of gas per 100 volumes of water at 20° C., and its aqueous solutions have a sour taste. The gas is liquefied easily; the liquid freezes at −56° C. under a pressure of about 5 atmospheres, forming a crystalline solid, dry ice, which sublimes at −78° C. Carbon Dioxide is official in the U.S.P.[7] It is used in mixtures with oxygen in artificial respiration. It is used to displace air from containers in which unstable chemicals or preparations are stored. Liquid carbon dioxide is used in fire extinguishers, and the solid form is used as a refrigerant.

When pure, silicon dioxide is a colorless, crystalline mass, but more commonly it is colored by the presence of foreign compounds, especially iron salts. It is used in countless industrial processes of an extremely wide variety. Purified Siliceous Earth U.S.P., also known as Kieselguhr and Diatomaceous Earth, is defined as consisting of the frustules and fragments of diatoms, purified by boiling with hydrochloric acid (to remove carbonates), washing and calcining.[8] Because it is an amorphous, soft mass, it is ideally suited as an abrasive in mild metal polishes and in dental cleansing agents.

Magnesium trisilicate is not the magnesium salt of silicic acid, as one might expect it to be. The official formula given in the U.S.P.[9] is $2MgO \cdot 3SiO_2 \cdot nH_2O$. It is used extensively in the treatment of peptic ulcers, being, according to some reports, the most efficient agent for this purpose because it gives physical protection to the wall of the stomach and controls the acid secretion over a period of about seven hours.

Titanium dioxide is a heavy white powder. It is described in an N.F. monograph,[10] but its use as a medicinal agent is questionable. It is most probable that official recognition is given to it because TiO_2 is used extensively in cosmetic preparations;[11] in powders and creams it is incorporated to enhance the white color of the preparation.

Tin dioxide also is a heavy white powder, but it is not used for application to the body in any form. Lead dioxide (lead peroxide) is a brown powder which is quite often used as an oxidizing agent; it is listed among the U.S.P. reagents.[12]

The dioxides of cerium and thorium are heavy dark powders, neither of which is used pharmaceutically.

TRIHYDROXIDES

The elements of the titanium subgroup are the only elements of group IV which can have an electropositive valence of 3, and this is because they are transition elements. When the valence is satisfied by the electronegative hydroxyl group, the trihydroxides result. For this subgroup, these are the ortho-ous acids.

ORTHO-OUS ACID	META-OUS ACID	"-OUS ACID" ANHYDRIDE
$Ti(OH)_3$......	$\mathrm{Ti}\Big\langle{}^{\mathrm{OH}}_{\mathrm{O}}$	Ti_2O_3
$Ce(OH)_3$......	$\mathrm{Ce}\Big\langle{}^{\mathrm{OH}}_{\mathrm{O}}$	Ce_2O_3
$Th(OH)_3$.....	$\mathrm{Th}\Big\langle{}^{\mathrm{OH}}_{\mathrm{O}}$	Th_2O_3

An extended discussion of the trihydroxides and their derivatives is not warranted because only the ortho acids and the acid anhydrides of titanium and cerium are known, the rest being hypothetical. Of those which are known, there are no important compounds, from the pharmacist's point of view, other than titanium trichloride, which is listed among the U.S.P. reagents.[12] Cerous sulfate [$Ce_2(SO_4)_3$], the sulfate of cerous hydroxide, is formed when ceric sulfate is reduced (p. 210).

It is worth noting that while there is an oxide of lead designated as Pb_2O_3, it is regarded as a complex of $PbO \cdot PbO_2$.

DIHYDROXIDES

The dihydroxides of the fourth group are formed from the elements of the carbon subgroup only. They are called the "-ous" acids. Therefore, while there is but one valence state (+4) for the "-ic" acids, there are 2 valence states for the "-ous" acids, namely, +2 for the carbon subgroup and +3 for the titanium subgroup. The ortho-ous acids and their dehydration products are listed summarily:

$\text{€}\Big\langle{}^{\mathrm{OH}}_{\mathrm{OH}}$ ORTHO-OUS ACID	$\text{€}{=}\mathrm{O}$ ORTHO-OUS ACID ANHYDRIDE (MONOXIDE)
$C(OH)_2$................ Orthocarbonous acid	CO Carbon monoxide
$Si(OH)_2$................ Orthosilicous acid	SiO Silicon monoxide
$Sn(OH)_2$............... Orthostannous acid	SnO Tin monoxide
$Pb(OH)_2$............... Orthoplumbous acid	PbO Lead monoxide

Occurrence. Representing the lowest state of valence for the elements, the dihydroxides are strong reducing agents; in other words, they are readily oxidized and consequently they never are found in nature as such. Orthocarbonous and orthosilicous acids are hypothetical compounds whose possible existence is suggested by their well-known anhydrides; the corresponding dihydroxides of tin and lead and salts of these hydroxides are well known.

Methods of Formation and Preparation.

I. HYDRATION OF THE CORRESPONDING OXIDE.

$$\text{€}{=}\mathrm{O} + H_2O \rightarrow \text{€}(OH)_2$$

Actually, the monoxides are so inactive that hydration of this sort perhaps never occurs. It seems to occur, however, when lead oxide or litharge is used in making lead plaster (see p. 224). Lead monoxide, however, reacts with alkali and the resulting compound yields orthoplumbous acid upon acidification.

$$PbO + KOH \rightarrow \mathrm{Pb}\Big\langle{}^{\mathrm{OH}}_{\mathrm{OK}}$$

$$Pb{<}^{OH}_{OK} + HCl \rightarrow Pb{<}^{OH}_{OH} + KCl$$

II. Alkaline Decomposition of the Corresponding Halide.

$$SnCl_2 + Na_2CO_3 + H_2O \rightarrow$$
$$Sn(OH)_2 + H_2O + CO_2 + 2NaCl$$

This reaction is not possible in the case of lead because $Pb(OH)_2$ reacts readily with CO_2. The lead acid is formed as an intermediate in the following reaction.

$$PbCl_2 + 2KOH \rightarrow Pb(OH)_2 + 2KCl$$
$$\downarrow$$
$$PbO + H_2O$$

III. Acidification of the Appropriate "-ite" Salt.

$$\mathcal{E}(OM)_2 + 2HX \rightarrow \mathcal{E}(OH)_2 + 2MX$$
$$Sn(ONa)_2 + 2HCl \rightarrow Sn(OH)_2 + 2NaCl$$

Properties. The ortho-ous acids, like the corresponding ortho-ic acids (excepting the acids of carbon), are flocculent precipitates when freshly formed. Orthoplumbous acid is very unstable, breaking down immediately into lead monoxide and water.

$$Pb(OH)_2 \rightarrow PbO + H_2O$$

The acids seemingly are dibasic, but they do not form both kinds of salts. For example:

$$Pb(OH)_2 + KOH \rightarrow Pb{<}^{OH}_{OK} + H_2O$$

$$Sn(OH)_2 + 2NaOH \rightarrow Sn(ONa)_2 + 2H_2O$$

The hydroxides are amphoteric. Their functioning as acids in reactions with alkalies has been demonstrated. They react with acids to form stable salts.

$$Sn(OH)_2 + 2HCl \rightarrow SnCl_2 + 2H_2O$$

In the case of tin, the stannous salts can be prepared in this manner because stannous hydroxide is a stable compound. Plumbous salts, however, must be prepared through the monoxide (see p. 224). Stannous chloride is listed among the U.S.P. reagents.[13] The instability of the salt is demonstrated by the fact that the test solution[14] must be freshly prepared and it must be preserved with a piece of metallic tin. The decomposition reaction proceeds as follows:

$$3SnCl_2 + H_2O + O \rightarrow 2Sn{<}^{OH}_{Cl} + SnCl_4$$

The hydrochloric acid solution of stannous chloride, which is more stable, is official also.[15] These solutions can be used in testing for the mercuric ion.

MONOXIDES

The monoxides are the acid anhydrides of the ortho-ous acids. Contrary to the situation prevailing for the dihydroxides from which they are derivable, the monoxides are well-known chemical compounds.

Occurrence. All of the monoxides are too active to occur naturally. When they are formed they unite with atmospheric gases, either oxygen or carbon dioxide, to form more stable compounds. (See under properties.) Carbon monoxide is a waste product of numerous metallurgic processes wherein the metallic oxide is reduced by elementary carbon. Illustrations are:

$$Fe_2O_3 + 3C \rightarrow 2Fe + 3CO$$
$$SnO_2 + 2C \rightarrow Sn + 2CO$$

The carbon monoxide is oxidized by atmospheric oxygen to the more stable carbon dioxide.

Lead, resulting from the natural decomposition of radium, may at one time have existed briefly as the monoxide. This, however, in contact with carbon dioxide of the atmosphere readily forms the lead carbonate, now serving as the ore of the metal.

$$2Pb + O_2 \rightarrow 2PbO$$
$$PbO + CO_2 \rightarrow PbCO_3$$

Methods of Formation and Preparation.

I. Dehydration of the Corresponding Ortho-ous Acid.

$$\mathcal{E}(OH)_2 \rightarrow \mathcal{E}O + H_2O$$

In most instances this takes place spontaneously; however, with stannous hydroxide it is necessary to apply heat very gently. If heated too strongly, the dioxide results.

$$Sn(OH)_2 \xrightarrow{\Delta} SnO + H_2O$$

II. Oxidation of the Corresponding Element with Limited Quantities of Oxygen.

$$2\mathcal{E} + O_2 \xrightarrow{\Delta} 2\mathcal{E}O$$

$$2C + O_2 \xrightarrow{\Delta} 2CO$$

$$2Si + O_2 \xrightarrow{\Delta} 2SiO$$

$$2Pb + O_2 \xrightarrow{\Delta} 2PbO$$

Metallic tin is not readily oxidized; however, carbon, silicon and lead are. Carbon monoxide is a product resulting from the spontaneous decay of organic matter (without free access to air), from destructive distillation reactions, from internal combustion engines, etc. Litharge or red lead (PbO) is produced commercially in the manner illustrated above.

III. Reduction of the Higher Oxide with Carbon.

$$\mathcal{E}O_2 + C \rightarrow 2\mathcal{E}O$$

$$CO_2 + C \xrightarrow{\Delta} 2CO$$

$$SiO_2 + C \xrightarrow{\Delta} SiO + CO$$

$$SnO_2 + C \xrightarrow{\Delta} SnO + CO$$

$$PbO_2 + C \xrightarrow{\Delta} PbO + CO$$

For the latter three dioxides, the reaction is difficult to control. However, reagent carbon monoxide is prepared on a large scale by passing the heated dioxide gas over hot carbon.

IV. Decomposition of an "-ite" Salt.

In a limited number of cases the monoxide can be produced by heating the metallic salt of a volatile oxyacid.

$$Pb(NO_3)_2 \xrightarrow{\Delta} PbO + NO + NO_2 + O_2$$

V. Pyrolytic Decomposition of Carbonyls.

$$Ni(CO)_4 \xrightarrow{\Delta} Ni + 4CO$$

Properties and Uses. Carbon monoxide is a colorless, odorless gas which is highly toxic to all forms of living matter. In the animal organism it combines with the hemoglobin and thereby interferes with the normal respiratory process. Its presence in motor vehicle engine exhaust brings it into direct daily contact with human beings the world over, and it therefore represents a potential major hazard. It is produced in pure form and marketed in steel drums, for use primarily in physiologic and pharmacologic experiments and in the manufacture of chemicals known as carbonyl compounds, e.g., $COCl_2$, carbonyl chloride; $(CO)_5Fe$, iron pentacarbonyl; $(CO)_6Co_2$, cobalt tricarbonyl. The question of the valence of the elements in carbon monoxide is a matter of open debate. The structural formula can be indicated in either of two ways, namely, $C{=}O$ and $C{\equiv}O$. Other than in carbon monoxide, divalent carbon is not known to exist. Tetravalent oxygen, on the other hand (see p. 18), is known to exist only in rare instances. Silicon monoxide is of no pharmaceutical or medicinal interest. It is a yellowish-brown solid which is used as a pigment and as an abrasive.

Tin monoxide (SnO) is a brown solid which reacts with both acids and alkalies.

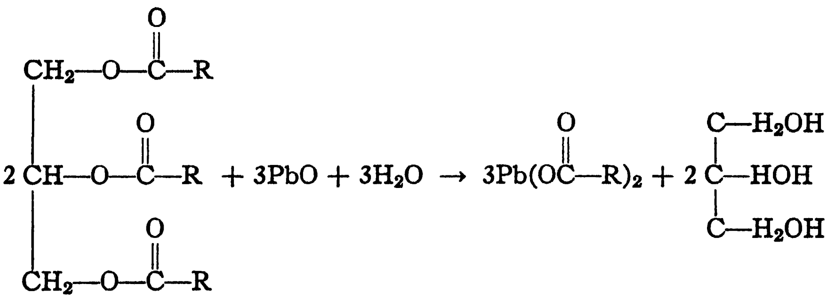
$$SnO + H_2SO_4 \rightarrow SnSO_4 + H_2O$$

$$SnO + KOH \rightarrow KHSnO_2$$

In alkaline solution, the stannites are powerful reducing agents.

Lead monoxide reacts similarly with acids and bases. However, it in itself is weakly basic. This property is utilized in preparing Lead Plaster[15] from Olive Oil, Lard and Lead Monoxide.[16] In the reaction, three molecules of (presumably) lead oleate are formed from the triglycerides. The ex-

tremely sticky lead soap is used as a medicated adhesive.



Glycerin

The lead salts usually contain the bivalent lead ion.

Official lead salts which are produced by the action of the appropriate acid on lead monoxide are shown in Table 36.

TABLE 36. OFFICIAL LEAD SALTS

NAME	FORMULA	USE
Lead Acetate U.S.P.	$Pb(C_2H_3O_2)_2 \cdot 3H_2O$	Astringent lotion, parasiticide
Lead Subacetate, U.S.P. Reagent	$Pb(C_2H_3O_2)_2 \cdot 2Pb(OH)_2$	Astringent and reagent
Basic Lead Carbonate, U.S.P. Reagent	$Pb(CO_3)_2 \cdot Pb(OH)_2$	Reagent
Lead Nitrate U.S.P.	$Pb(NO_3)_2$	Reagent

All soluble lead compounds, of which there are few, are poisonous. Some insoluble ones, such as the oxide, can cause poisoning through prolonged contact with the skin. In this process it is possible that the organic acids which remain on the skin following evaporation of the perspiration react with the oxide to form fat-soluble salts which are absorbed through the skin.

$$Pb\boxed{O + 2H}OOC{-}R \rightarrow Pb{-}(OOC{-}R)_2 + H_2O$$

Lead is said to be a cumulative poison. Traces of it are picked up by the body from time to time in the form of insecticides incompletely removed from plant foods or from excessive contact with lead-pigmented paints. It accumulates in the fatty tissues of the body until the tolerance limits are exceeded, whereupon symptoms of poisoning result.

Soluble lead salts are incompatible with soluble chlorides, carbonates, sulfates and phosphates; with these compounds they yield insoluble precipitates of the corresponding lead compounds.

OTHER HYDROXY ACIDS

A small number of acids which do not fit into the system of classification used for the hydroxides of group IV elements are known. Reference was already made (p. 214) to the existence of polystannic and polytitanic acids. Some of silicic acids have been prepared, while others are hypothetical, their existence being assumed on the basis of known salts.

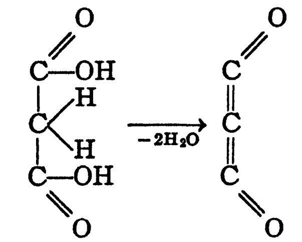
NAME	FORMULA
Orthodisilicic acid	$H_6Si_2O_7$ or $2SiO_2 \cdot 3H_2O$
Metadisilicic acid	$H_2Si_2O_5$ or $2SiO_2 \cdot H_2O$
Orthotrisilicic acid	$H_8Si_3O_{10}$ or $3SiO_2 \cdot 4H_2O$
Orthotetrasilicic acid	$H_{10}Si_4O_{13}$ or $4SiO_2 \cdot 5H_2O$

β-Metastannic acid ($H_{10}Sn_5O_{15}$) might be regarded a polystannic acid. Chemically, however, it reacts like metastannic acid.

OTHER OXIDES

Just as there are hydroxides which do not fit the system of uniformity, so are there oxides of some of the elements of group IV which cannot be classified.

According to reference tables, carbon forms a suboxide (C_3O_2) whose graphic formula is O=C=C=C=O. It is called di-oxopropadiene.



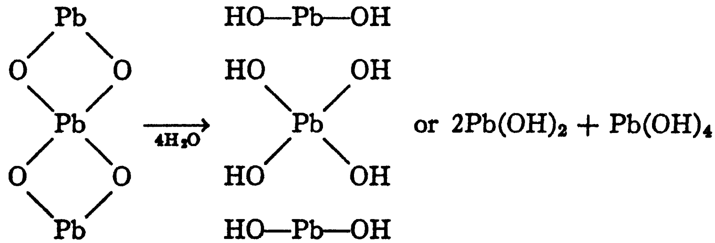
Malonic Acid Di-oxopropadiene

If this interpretation holds true, it would seem that the number of oxides of carbon which could exist is equally great.

There exists an oxide of lead, Pb_3O_4, which is regarded by some as a combination of $2PbO$ and PbO_2. It can be prepared by the following reaction:

$$K_2PbO_3 + 2K_2PbO_2 + 3H_2O \rightarrow Pb_3O_4 + 6KOH$$

Pb_3O_4 is regarded as evidence for the existence of orthoplumbic acid, $Pb(OH)_4$, because of this relationship:



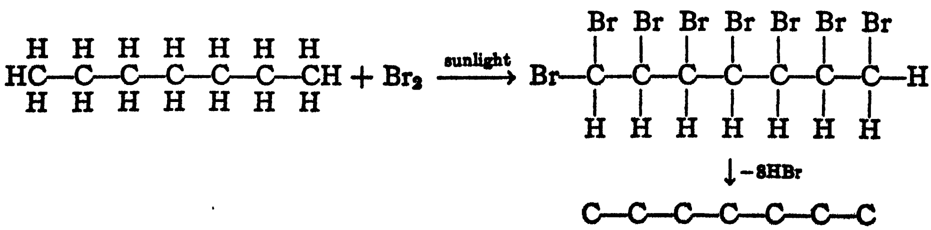
Some investigators are of the opinion that there are many allotropic forms of carbon, ranging from C_1, C_2, C_3, C_4, etc., to no known end. To them, the carbon nucleus of each and every different organic compound represents a different form of C_x. Schorlemmer is credited with being among the first to take this point of view; he attempted, without success, to prepare C_7 from normal heptane in the following manner:

When lead monoxide is oxidized in alkaline solution, the trioxide results:

$$2PbO + NaClO \xrightarrow{KOH} Pb_2O_3 + NaCl$$

Pb_2O_3, an orange-yellow powder, could be a compound oxide, $PbO \cdot PbO_2$.

Titanium forms a number of oxides, two of which (TiO_2 and Ti_2O_3) have been mentioned. In addition, it forms the monoxide (TiO) and the trioxide (TiO_3).



REFERENCES

1. U.S.P. XIII, p. 828.
2. *Ibid.*, pp. 755 and 854.
3. *Ibid.*, pp. 485 and 421.
4. *Ibid.*, p. 294.
5. *Ibid.*, p. 659.
6. *Ibid.*, p. 299.
7. *Ibid.*, pp. 111-112.
8. *Ibid.*, p. 473.
9. *Ibid.*, p. 299.
10. N.F. VIII, p. 537.
11. *Ibid.*, p. 524.
12. U.S.P. XIII, p. 771.
13. *Ibid.*, p. 777.
14. *Ibid.*, p. 825.
15. *Ibid.*, p. 844.
16. N.F. VIII, p. 294.

14

Elements of Group III

ELEMENTS
HYDRIDES OF BORON
HYDROXIDES (OXYACIDS) AND THEIR SALTS
TRIHYDROXIDES
MONOXIDE MONOHYDROXIDES
TRIOXIDES
OTHER HYDROXY ACIDS

ELEMENTS

Group III of the periodic system embraces 9 elements, 2 of which are very important and common and 7 of which are unimportant and very rare. The former are boron and aluminum (aluminium), while the latter group includes scandium, gallium, yttrium, indium, lanthanum, thallium and actinium. In order to provide a composite picture of the entire group, the elements and some of their properties are shown in Table 37.

physical properties, gallium is outstanding among these elements because it is a liquid (m.p. 29.75° C.). Actinium is unusual because of its radioactivity.

Other than boron and aluminum, the elements of this group have no pharmaceutical interest; consequently, the properties of the other elements and their compounds will not be considered here.

History. As has happened in numerous instances, several investigators have worked in the same field of research simultaneously and independently, and their results frequently have been published at the same time. Gay-Lussac and Thenard collaborated in their work on boron; however, Sir Humphry Davy worked independently of them. In 1807, while engrossed in the study

TABLE 37. ELEMENTS OF GROUP III

NAME	SYMBOL	AT. WT.	AT. NO.	DENSITY	ISOTOPES
Boron	B	10.82	5	2.3 (cryst.)	10, 11
Aluminum	Al	26.97	13	2.702	None known
Scandium	Sc	45.10	21	3.02	None known
Gallium	Ga	69.72	31	6.093 [32]	69, 71
Yttrium	Y	88.92	39	5.51	None known
Indium	In	114.76	49	7.3	113, 115
Lanthanum	La	138.92	57	6.15	None known
Thallium	Tl	204.39	81	11.85	201, 202, 203, 204, 205, 207, 209, 211, 213, 215
Actinium	Ac	229.–	89	......	None known

An electropositive valence of 3 is characteristic of most of the elements, although thallium regularly shows a valence of +1 and gallium occasionally has shown a valence of +2. From the point of view of

of the alkalies, Davy passed an electric current through boric acid. He noticed the accumulation of a brown substance at the negative electrode, but he did not investigate it further. During the following year, he and Gay-Lussac and Thenard isolated boron from a mixture of boric acid and potassium which had been fused in a copper tube. The French chemists are credited with the discovery since the results of their work were published first, on June 21, 1808, while Davy's paper announcing the discovery of metallic boron was read before the Royal Society on June 30, 1808.

The discovery of aluminum involved a number of famous persons, beginning with George Ernst Stahl, who, with Johann Becher, originated the phlogiston theory (p. 20). Stahl believed that alum contained a peculiar base, and Marggraf proved this was different from all others. Berzelius and Davy were unsuccessful in their attempts to isolate the element by electrolysis of alumina. Oersted, the famous physicist, first prepared aluminum chloride by passing chlorine over a heated mixture of charcoal and alumina. By allowing potassium amalgam to react with the aluminum chloride, he obtained an aluminum amalgam from which he distilled the mercury. The reactions are illustrated in the following equations:

$$Al_2O_3 + 3C + 3Cl_2 \rightarrow 2AlCl_3 + 3CO$$

$$AlCl_3 + 3KHg \rightarrow AlHg + 3KCl$$

$$AlHg \xrightarrow{\Delta} Al + Hg$$

Wöhler was unable to prepare pure aluminum by Oersted's method and he attributed the failure to the presence of water in the aluminum chloride. The moisture presumably reacted with the potassium amalgam to form potassium hydroxide, which, when heated, attacked the free aluminum. He prepared anhydrous aluminum chloride by heating a mixture of charcoal, sugar and oil with freshly precipitated, dried aluminum hydroxide in an atmosphere of dry chlorine gas. Metallic aluminum was isolated from the chloride by fusion with potassium. Wöhler is generally credited with the discovery of aluminum, but Oersted's contribution cannot be ignored.

Occurrence. Boron never occurs in the free state. Compounds of it occur in extensive deposits in a number of places, especially where lakes and inland seas have dried up. German sources yield *boracite*, $2Mg_3B_8O_{15} \cdot MgCl_2$, while the U. S. deposits in California and Nevada yield *kernite*, $Na_2B_4O_7 \cdot 4H_2O$; *borax*, $Na_2B_4O_7 \cdot 10H_2O$, and *colemanite*, $Ca_2B_6O_{11} \cdot 5H_2O$.

Mention has already been made (p. 204) of native forms of aluminum silicates, including Pumice N.F., Talcum U.S.P., Bentonite U.S.P., and other clays which are found all over the world. Aluminum is the most abundant metal to be found in the earth's crust. The principal ore is *bauxite*, a mixture of $Al_2O_3 \cdot H_2O$ and $Al_2O_3 \cdot 3H_2O$. Because of its use in refining the ore, cryolite (Na_3AlF_6) is of considerable importance. It is obtained principally from Greenland, although large quantities are produced artificially. The hydrated oxide ores occur extensively in the south-central United States and the Pacific northwest.

Methods of Preparation. In a few instances, the methods for isolating free boron and free aluminum are parallel.

I. Reduction of Appropriate Compounds by the Action of Alkali Metals and Heat.

$$B(OH)_3 + 3K \xrightarrow{\Delta} B + 3KOH$$

$$AlCl_3 + 3K \xrightarrow{\Delta} Al + 3KCl$$

These reactions were employed by the original investigators for the isolation of the elements. Technically, they are still applicable; however, less expensive reducing agents have been substituted. For example, commercial production of boron utilizes the reducing powers of aluminum and magnesium.

$$B_2O_3 + 2Al \rightarrow 2B + Al_2O_3$$

$$B_2O_3 + 3Mg \rightarrow 3MgO + 2B$$

In the latter reaction, an excess of magnesium must be avoided so that magnesium boride (like magnesium silicide) is not formed.

II. Electrolytic Decomposition of the Double Halides.

$$KBF_4 + 3Na \xrightarrow[\text{elect.}]{} B + KF + 3NaF$$

$$NaAlCl_4 + 3K \xrightarrow[\text{elect.}]{} Al + NaCl + 3KCl$$

These methods very likely evolved from the Hall process for producing aluminum, which was originated in 1886. Hall's method for the electrolytic decomposition of aluminum ores utilized a large iron vat lined with carbon (coke) which serves as the cathode ($-$). A charge of purified aluminum oxide and cryolite, intimately mixed, is placed into the vat or crucible, and the anodes are lowered into it. The resistance of the charge to the passage of electricity produces sufficient heat to fuse the mass into a liquid. The molten aluminum accumulates at the bottom and so it can be drawn off easily.

Bauxite, the chief aluminum ore, contains impurities of iron and titanium which are carried through into the finished product. Therefore, it is customary to purify the ore by treating it with concentrated sodium hydroxide solution, whereupon the aluminum dissolves in the form of sodium aluminate ($NaAlO_2$), while the hydroxides of iron and titanium precipitate. The solution is filtered and diluted with water, causing hydrated forms of Al_2O_3 to precipitate. When dried, this constitutes the purified aluminum oxide used in the process.

Physical Properties. Not too much is known of the properties of boron because of the great difficulty in obtaining the element in the pure state. It has a tendency to combine with the reducing agents used. Crystalline boron is said to be colorless, resembling diamond in hardness and brilliance. Usually, it is represented by a brown microcrystalline powder called amorphous boron. Both forms are poor conductors of electricity at ordinary temperatures, but the conductivity increases with the increase in temperature. This property is not characteristic of the metals. It melts at 2,300° C. and sublimes at 2,550° C.

Compared with iron, copper and other common metals, the density of aluminum is low; it therefore is classified as a light metal. Ordinarily, aluminum is soft, ductile and malleable; however, as it is heated it becomes brittle, and just below its melting point (670° C.) it can be ground to a powder. It is an excellent conductor of both heat and electricity and it commonly is used in devices which are adapted to these properties. The metal is silvery white. It loses its high luster upon exposure to the air, due to the formation of a thin coating of the oxide.

Chemical Properties. Boron is classified as a metalloid. Its chemical properties show it to be more closely related to carbon and silicon than it is to aluminum. In all of its known compounds it exhibits valence of $+3$ and -3, with the electropositive valence predominating. At ordinary temperatures it resists oxidation by both elementary oxygen and nitric acid. At 100° C. it oxidizes slowly and at 700° C. it ignites in oxygen, burning with a green flame.

$$4B + 3O_2 \xrightarrow{\Delta} 2B_2O_3$$

Boron itself is a strong reducing agent. When heated with nitric acid, sulfuric acid, ferric compounds and other oxidizing agents, it is converted to orthoboric acid, H_3BO_3. Like carbon and silicon, it forms hydrides, called boranes, which are powerful reducing agents.

The element combines directly with the halogens, except iodine, to form compounds having the general formula BX_3. They are used as catalysts in organic chemistry. Boron trifluoride (BF_3) is formed at room temperature through the spontaneous ignition of boron in an atmosphere of fluorine. Heat is required to cause boron to combine

with chlorine and with bromine. When boron is heated with sulfur, boron trisulfide (B_2S_3) results. It is one of the few elements which combines directly with nitrogen, forming the nitride, BN. At the temperature of the electric arc, boron and carbon unite, forming boron carbide, B_6C. At elevated temperatures, the element combines with a variety of metals to form the corresponding metallic borides.

When elementary boron is dissolved in fused alkalies, borates are formed:

$$2B + 6NaOH \rightarrow 2Na_3BO_3 + 3H_2$$

Aluminum is an active metal. It oxidizes slowly at room temperature, forming the oxide Al_2O_3. When the powdered metal is burned in an atmosphere of oxygen, it emits an intense white light in being converted to the oxide. If the powdered metal is burned in air, both the oxide and the nitride (AlN) result. This affinity for oxygen is utilized in the thermite or Goldschmidt process, which is employed in welding iron and steel. The reaction, producing molten iron, is as follows:

$$2Al + Fe_2O_3 \rightarrow Fe + Al_2O_3$$

Aluminum is not active enough to combine directly with hydrogen. However, when the metal is heated, it combines with a number of other elements, including chlorine and the other halogens, sulfur, phosphorus and carbon.

$$2Al + 3Cl_2 \xrightarrow{\Delta} 2AlCl_3 \quad \text{or} \quad Al_2Cl_6$$

$$2Al + 3S \xrightarrow{\Delta} Al_2S_3$$

$$Al + P \xrightarrow{\Delta} AlP$$

$$4Al + 3C \xrightarrow{\Delta} Al_4C_3$$

Nonoxidizing acids, such as hydrochloric, are decomposed by aluminum,

$$2Al + 6HCl \rightarrow 2AlCl_3 + 3H_2$$

With nitric and sulfuric acids the evolution of hydrogen is very slight. Its reaction with strong bases is vigorous.

$$2Al + 2NaOH + 2H_2O \rightarrow 2NaAlO_2 + 3H_2$$

HYDRIDES OF BORON

Boron resembles carbon and silicon in that it forms a number of hydrides. The union between boron and hydrogen does not take place directly. They can be caused to unite in the following manner:

$$B_2Hg_3 + 6HCl \rightarrow 2BH_3 + 3HgCl_2$$

The simplest boron hydride, BH_3, supposedly is too active to exist as such, consequently it polymerizes to form B_2H_6. The known boron hydrides or boranes are the following:

Diborane (boro-ethane).........	B_2H_6
Tetraborane (borobutane).......	B_4H_{10}
Pentaborane...................	B_5H_9
Hexaborane....................	B_6H_{11}
Decaborane....................	$B_{10}H_{14}$

The boranes are powerful reducing agents, the lower members reacting with explosive violence.

Aluminum does not form binary compounds with hydrogen, but it does form the ternary compound, $LiAlH_4$, which is used in the reduction of oxygenated organic compounds.

HYDROXIDES (OXYACIDS) AND THEIR SALTS

Being trivalent, boron and aluminum form trihydroxides which are the oxyacids of the elements. They and their dehydration products are tabulated as follows:

$\cancel{\mathrm{R}}(OH)_3$ TRIHYDROXIDE ORTHO-IC ACID	$\cancel{\mathrm{R}}O(OH)$ MONOXIDE, MONOHYDROXIDE META-IC ACID	$\cancel{\mathrm{R}}_2O_3$ TRIOXIDE ACID ANHYDRIDE
$B(OH)_3$.......... Orthoboric acid	$BO(OH)$ Metaboric acid	B_2O_3 Boron oxide
$Al(OH)_3$......... Ortho-aluminic acid	$AlO(OH)$ Meta-aluminic acid	Al_2O_3 Aluminum oxide

The acids and the oxides listed above are well-known compounds; however, only the ortho-acids and their derivatives are of pharmaceutical importance.

TRIHYDROXIDES

Occurrence. Orthoboric acid occurs naturally to a limited extent in the hot spring waters of Italy's volcanic region. Salts of it are widely distributed on the surface of the earth.

Ortho-aluminic acid is too active to occur naturally, but compounds derived from it are common.

Methods of Formation and Preparation. General reactions for the preparation of the ortho-acids of boron and aluminum are few in number.

I. Hydration of the Acid Anhydride.

$$B_2O_3 + 3H_2O \rightarrow 2B(OH)_3$$

$$Al_2O_3 + 3H_2O \rightarrow 2Al(OH)_3$$

The actual hydration of Al_2O_3 is questionable; however, the freshly precipitated oxide in water reacts like the hydroxide with respect to acids and bases. This hydration is accomplished indirectly through the use of aqueous alkali, for example:

$$Al_2O_3 + 2NaOH \rightarrow 2NaAlO_2 + H_2O$$

$$B_2O_3 + 2NaOH \rightarrow 2NaBO_2 + H_2O$$

The resulting solution of the meta-acid salt yields the ortho-acid upon dilution (p. 233).

$$NaAlO_2 + 2H_2O \rightarrow Al(OH)_3 + NaOH$$

II. Hydrolysis of Unstable Salts.

$$BCl_3 + 3H_2O \xrightarrow{\Delta} B(OH)_3 + 3HCl$$

$$AlCl_3 + 3H_2O \rightarrow Al(OH)_3 + 3HCl$$

$$Al_2(SO_4)_3 + 6H_2O \rightarrow 2Al(OH)_3 + 3H_2SO_4$$

These salts of boron and aluminum have a strongly acidic reaction when dissolved in water, indicating the hydrolysis shown above. If the mineral acid formed is volatile (HCl), it can be driven off, leaving the trihydroxide in suspension.

III. Decomposition of a Stable Salt.

$$Na_2B_4O_7 \cdot 10H_2O + 2HCl \rightarrow 2NaCl + 4B(OH)_3 + 5H_2O$$

$$2KAl(SO_4)_2 \cdot 12H_2O + 6NH_4OH \rightarrow K_2SO_4 + 3(NH_4)_2SO_4 + 2Al(OH)_3 + 12H_2O$$

The first equation demonstrates the commercial and the laboratory methods for the preparation of boric acid.

For pharmaceutical purposes, the quality of aluminum hydroxide is dependent upon the state of subdivision. A more active compound is obtained by treating the aqueous solution of an alum with dilute sodium carbonate solution. Sodium carbonate hydrolyzes sufficiently to yield sodium hydroxide, which is the active base in decomposing the alum.

$$Na_2CO_3 + 2H_2O \leftrightharpoons 2NaOH + H_2CO_3$$

$$2KAl(SO_4)_2 \cdot 12H_2O + 6NaOH \rightarrow K_2SO_4 + 3Na_2SO_4 + 2Al(OH)_3 + 12H_2O$$

An excess of the base must be avoided, for the $Al(OH)_3$ will react with it to a certain extent.

$$Al(OH)_3 + NaOH \rightarrow NaAlO_2 + 2H_2O$$

IV. Reaction of the Element with Caustic Alkali and the Decomposition of the Resulting Salt.

$$2B + 6NaOH \xrightarrow[\Delta]{\text{fuse}} 2Na_3BO_3 + 3H_2$$

$$Na_3BO_3 + 3HCl \rightarrow H_3BO_3 + 3NaCl$$

$$2Al + 6KOH \xrightarrow{\Delta} 2Al(OK)_3 + 3H_2$$

$$Al(OK)_3 + 3HCl \rightarrow Al(OH)_3 + 3KCl$$

Properties and Salts. Boric Acid U.S.P.,[1] also known as orthoboric acid and boracic acid, is available in either of two forms, namely, the crystalline and the so-called powdered form, which actually is microcrystalline. The larger crystals are in the form of platelets which are soft and waxy to the touch. It is odorless, colorless (in

crystalline form) and stable in the air. While Boric Acid Solution is official in the N.F.,[2] it frequently is prepared by the layman because of its extensive application as a very mild antiseptic for open wounds and for the delicate membranes of the eye. At 20° C., 4.96 grams of the acid dissolve in 100 cc. of water. The solubility is higher at elevated temperatures, e.g., 25 Gm./100 cc. at 100° C. The rate of solution is an important consideration.

Contrary to the general laws concerning solubility, wherein the surface area of the solute is a factor determining in part the rate of solution, powdered boric acid dissolves more slowly than does the crystalline form. This is due to the fact that boric acid forms an unwettable powder. When put into water, it resists all attempts to distribute it throughout the solvent. Patient heating and stirring result in a clear solution. Boric acid solution intended for ophthalmic purposes should be filtered free of crystals before being used or dispensed.

In itself, boric acid is a weak antiseptic; however, when combined with other soluble borates, borax, for example, the germicidal properties become quite pronounced. Excessive quantities of boric acid solution taken internally have caused numerous deaths, especially among infants. Boric Acid Ointment[3] is intended for application to small wounds and abraded skin because of its soothing effect and mild antiseptic properties.

Boric acid is but slightly amphoteric. It would seem that it should act as a weak base toward strong acids such as HCl, HBr, etc.; however, the salts, BCl_3, BF_3, etc., are readily decomposed by water. When it is necessary to produce the halides, they are made by treating the oxide with the gaseous hydrohalogen.

$$B_2O_3 + 6HF \rightarrow 2BF_3 + 3H_2O$$

or by:

$$B_2O_3 + 3C + 3Cl_2 \rightarrow 2BCl_3 + 3CO$$

These salts are readily decomposed by water as illustrated:

$$BF_3 + 3H_2O \rightarrow B(OH)_3 + 3HF$$

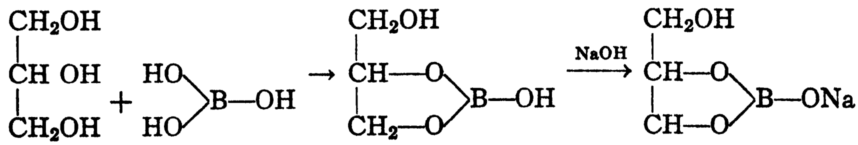
With alkalies, orthoboric acid forms unstable (in solution) salts.

$$H_3BO_3 + 3NaOH \rightarrow Na_3BO_3 + 3H_2O$$

$$Na_3BO_3 + H_2O \rightarrow NaBO_2 + 2NaOH$$

$$NaBO_2 + 2H_2O \rightarrow H_3BO_3 + NaOH$$

For this reason, boric acid cannot be assayed by direct titration with alkali, as the end point appears prematurely, due both to the alkalinity of sodium metaborate and the liberation of sodium hydroxide in the decomposition of trisodium orthoborate. According to Pharmacopœial directions,[3] glycerin is added to a sample of boric acid in solution prior to the titration.

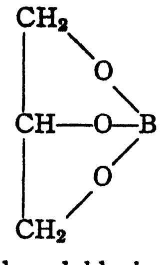


Glycerin   Glyceryl Boric Acid
Glyceryl Monoborate

This results in the formation of a double ester, namely, glyceryl boric acid, which ionizes far more strongly than does boric acid itself. Furthermore, the possibility of forming metaboric acid and its salts is precluded.

A reaction of this type is utilized in pharmaceutical practice in making a water-soluble form of boric acid, Boroglycerin Glycerite U.S.P.[4] Boroglyceride is a compound of indefinite composition formed by heating glycerin and boric acid at 140° to

150° C. Its formula is assumed to be $C_3H_5BO_3$, which, indicated structurally, would be



It is completely soluble in water, and its solution is acidic to litmus paper. Usually it is applied to the body in the form of suppositories.[5]

The trihydroxide of aluminum also is amphoteric. It is stronger as a base than it is as an acid; consequently, it is commonly called aluminum hydroxide rather than aluminic acid. In the moist state it is a gelatinous, opalescent mass which can be dried to a white powder. Though it is insoluble in water, it ionizes sufficiently to yield both an acid and an alkaline reaction with litmus paper. It has an astringent taste, characteristic of the aluminum salts.

Aluminum Hydroxide Gel (containing 4 per cent Al_2O_3) and Dried Aluminum Hydroxide Gel (containing not less than 50 per cent of Al_2O_3) are official in the U.S.P.[6] Both are employed in the treatment of excessive gastric acidity and gastric ulcers. The former is marketed as a creamy suspension of $Al(OH)_3$, either plain or flavored, and the latter is compressed into large wafers. The quality of either form of the medicament is determined on the basis of the amount of tenth-normal hydrochloric acid which it can neutralize in a period of one hour at body temperature, 37.5° C.

Alumina cream, as the hydroxide is commonly known, has long been used in water purification. When added to water which contains suspended matter, the aluminum hydroxide settles out as a gelatinous precipitate, occluding and carrying down the suspended foreign matter. Water from which aluminum hydroxide has settled is sparklingly clear and it has a slightly astringent taste. Due to its colloidal nature, aluminum hydroxide can be employed very effectively in clogging the pores of filters used in clarifying liquids, such as parenteral solutions. It must be noted, however, that the solutions to which $Al(OH)_3$ is added can be neither strongly acidic nor strongly basic.

When treated with a base, aluminum hydroxide forms the meta-aluminate as the final reaction product. The reaction takes place in two steps:

$$Al(OH)_3 + 3KOH \rightarrow Al(OK)_3 + 3HOH$$

$$Al(OK)_3 + H_2O \rightarrow AlO(OK) + 2KOH$$

In this respect, the behavior of aluminic acid is identical with that of boric acid.

Aluminum hydroxide reacts readily with strong acids, forming salts which are extremely soluble in water and whose solutions have a strong acid reaction. Thus:

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$$

This salt is very unstable and the presence of water tends to reverse the reaction:

$$AlCl_3 + 3H_2O \rightarrow Al(OH)_3 + 3HCl$$

Therefore it cannot be employed in the production of aluminum chloride. Commercially, the anhydrous salt is prepared in the following manner:

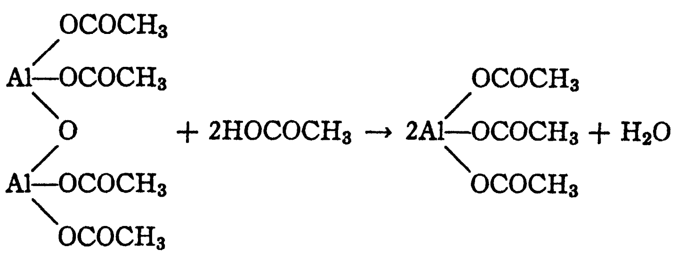
$$Al_2O_3 + C + 3Cl_2 \rightarrow 2AlCl_3 \quad \text{or} \quad Al_2Cl_6 + 3CO$$

Below 150° C., the density of its vapor indicates the molecular formula to be Al_2Cl_6. The anhydrous salt, purified by sublimation, is used as a catalyst in several types of reactions in organic chemistry. It forms double salts such as $AlCl_3 \cdot NaCl$, $AlCl_3 \cdot PCl_5$ and $AlCl_3 \cdot SCl_4$.

Aluminum Chloride N.F.[7] ($AlCl_3 \cdot 6H_2O$) is a powerful astringent. It is used in deodorant preparations. Being an astringent, it causes the pores of the skin to close, thus retarding the flow of perspiration. In addition, the liberation of HCl by the hydrolysis

of the salt prevents the bacterial decomposition of perspiration residues.

The ease of hydrolysis and the subsequent loss of acetic acid accounts for the fact that aluminum acetate has not been isolated. Aluminum Acetate Solution N.F.,[8] is prepared through aluminum subacetate by means of this reaction:



On the other hand, Aluminum Subacetate Solution N.F.[9] is prepared through the following reactions:

$$Al_2(SO_4)_3 + 3CaCO_3 + 3H_2O \rightarrow 2Al(OH)_3 + 3CaSO_4 + 3CO_2$$

$$2Al(OH)_3 + 4CH_3COOH \rightarrow Al_2O(OOCCH_3)_4 + 4H_2O$$

Both of the official solutions are used as astringent lotions and antiseptic washes.

With sulfuric acid, aluminum hydroxide forms aluminum sulfate, which is a strong acidic salt.

$$2Al(OH)_3 + 3H_2SO_4 \rightarrow Al_2(SO_4)_3 + 6H_2O$$

Aluminum Sulfate N.F.[10] is in itself not an unusual chemical, but the compounds which it forms with other soluble sulfates, e.g., the alkali sulfates, are unusual. They are called alums. Thus,

$$Na_2SO_4 + Al_2(SO_4)_3 + 24H_2O \rightarrow Na_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$$

and

$$(NH_4)_2SO_4 + Al_2SO_4 + 24H_2O \rightarrow (NH_4)_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$$

Elements other than aluminum form alums; there are ferric alums, chrome alums and cobalt alums. They can be defined as the sulfate of a monovalent metal together with the sulfate of a trivalent metal and 24 molecules of water of crystallization. Their formulae generally can be indicated as $M'_2SO_4 \cdot M'''_2(SO_4)_3 \cdot 24H_2O$; however, in modern practice some texts use the half-formula. For example, by definition the formulae for Potassium Alum and Ammonium Alum would be twice that now used in the U.S.P.[11]

Old Formula	U.S.P. Formula
$(NH_4)_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$...	$NH_4Al(SO_4)_2 \cdot 12H_2O$
$K_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$......	$KAl(SO_4)_2 \cdot 12H_2O$

The alums are prepared by bringing together aqueous solutions containing mole equivalents of the two salts and allowing crystallization to occur. The alums are noted for their splendid crystalline structure.

Both ammonium alum and potassium alum are recognized under the U.S.P. term Alum. In pharmacy, when one particular variety is specified, it must be used to the exclusion of the other. Generally, they can be used interchangeably. Alum is used as a styptic and hemostatic. Due to the variability of the water content of the alums under different atmospheric conditions, the U.S.P. recognizes dehydrated forms under the names Exsiccated Alum, Dried Alum and Burnt Alum.[12] Dried Alum is capable of producing burns when applied to the skin, so great is its affinity for water.

In pharmaceutical industry, alum is used in preparing Alum Precipitated Diphtheria and Tetanus Toxoids U.S.P.,[13] and Alum Precipitated Tetanus Toxoid U.S.P.[14] Alum

is used in purifying these toxoids because it provides a more complete separation of the toxoid from the other proteinic matter present. Furthermore, an alum precipitated toxoid is approximately twice as active as toxoids purified by other means.

Aluminum hydroxide reacts with phosphoric acid, forming a gelatinous precipitate containing about 4 per cent of $AlPO_4$. Aluminum Phosphate Gel U.S.P.[15] is used in treating gastric ulcers and is regarded as superior to Aluminum Hydroxide Gel by some physicians.

MONOXIDE MONOHYDROXIDES

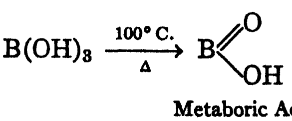
The monoxide monohydroxides of boron and aluminum are the meta-acids of the elements. They do not occur in nature in any form. Though the acid itself cannot be isolated, salts of meta-aluminic acid are formed readily. For example,

$$Al_2O_3 + 2NaOH \rightarrow 2NaAlO_2 + H_2O$$

When aluminum hydroxide is heated, the meta-acid might be formed as an intermediate; however, it has not been isolated, as the reaction invariably proceeds to the trioxide stage.

$$2Al(OH)_3 \xrightarrow{\Delta} [2AlO(OH)] \xrightarrow{\Delta} Al_2O_3$$

When boric acid is heated to 100° C., metaboric acid results. If the temperature reaches 140° C., pyroboric acid is formed.



Metaboric Acid

The sodium salt of metaboric acid is formed when an aqueous solution of borax is treated with sodium peroxide or with sodium hydroxide and hydrogen peroxide. The official name, Sodium Perborate,[16] would lead one to believe that the compound is a peroxide. Actually it is sodium metaborate with both hydrogen peroxide and water of crystallization. Its formula is indicated as $NaBO_2 \cdot H_2O_2 \cdot 3H_2O$. It is a colorless, crystalline compound which is poorly soluble in cold water, but is decomposed by it, releasing hydrogen peroxide (p. 108). It is a constituent of numerous dentifrice powders. Because of its instability, it is not suitable as an oral antiseptic in liquid form.

TRIOXIDES

The trioxides of boron and aluminum have no direct application in pharmacy.

OTHER HYDROXY ACIDS

Boron forms numerous other hydroxy acids, most of which are known only through their salts. They can be regarded hydrates of boron trioxide, as illustrated in the following tabulation:

$H_2B_2O_4$	or	$H_2O \cdot B_2O_3$
$H_2B_4O_7$		$H_2O \cdot 2B_2O_3$
$H_6B_4O_9$		$3H_2O \cdot 2B_2O_3$
$H_2B_6O_{10}$		$H_2O \cdot 3B_2O_3$

The second one in the list, $H_2B_4O_7$, is one of the few acids of boron known to exist. When orthoboric acid is heated to 100° C. it loses water to form the meta-acid,

$$H_3BO_3 \xrightarrow[\Delta]{100^\circ C.} HBO_2 + H_2O$$

At 140° C., the meta-acid is further dehydrated, yielding the so-called pyroboric acid. It is known also as tetraboric acid.

$$4HBO_2 \xrightarrow[\Delta]{140^\circ C.} H_2B_4O_7 + H_2O$$

Tetraboric acid (pyroboric acid, biboric acid) occurs naturally in the form of sodium tetraborate (borax). However, when sodium tetraborate is decomposed with hydrochloric acid, orthoboric acid results instead of tetraboric acid.

$$Na_2B_4O_7 \cdot 10H_2O + 2HCl \rightarrow 2NaCl + H_2B_4O_7 + 10H_2O$$

$$H_2B_4O_7 + 5H_2O \rightarrow 4H_3BO_3$$

Pure sodium tetraborate is prepared by treating sodium metaborate with carbon dioxide.

$$4NaBO_2 + CO_2 \rightarrow Na_2B_4O_7 + Na_2CO_3$$

In the Pharmacopœia, sodium tetraborate is known as Sodium Borate.[17] It is a white powder, odorless and stable in the air. Aqueous solutions of it are alkaline in reaction and are used as an alkaline wash. The compound is used extensively as a water softener because of the alkali liberated when it is dissolved in water.

$$Na_2B_4O_7 + 3H_2O \rightleftharpoons 2NaBO_2 + 2H_3BO_3$$

$$NaBO_2 + 2H_2O \rightleftharpoons NaOH + H_3BO_3$$

Sodium tetraborate is an important reagent in qualitative analysis. Compounds of chromium, manganese, iron, etc., form glassy metaborates when fused with borax, and the glassy bead imparts a characteristic color to a flame. It also is used in making strain-resistant glass (Pyrex) in which it serves to reduce the coefficient of expansion of the glass. Furthermore, it reduces the tendency toward crystallization and increases the refractive index of glass.

REFERENCES

1. U.S.P. XIII, pp. 82 and 748.
2. N.F. VIII, p. 88.
3. U.S.P. XIII, p. 83.
4. *Ibid.*, p. 84.
5. N.F. VII, p. 399.
6. U.S.P. XIII, pp. 26 and 27.
7. N.F. VII, p. 37.
8. *Ibid.*, p. 36.
9. *Ibid.*, p. 38.
10. N.F. VIII, p. 39.
11. U.S.P. XIII, p. 24.
12. *Ibid.*, p. 25.
13. *Ibid.*, p. 184.
14. *Ibid.*, p. 559.
15. *Ibid.*, p. 28.
16. *Ibid.*, p. 501.
17. *Ibid.*, p. 486.

15

Elements of Group II

BERYLLIUM AND MAGNESIUM
THE ALKALINE EARTH METALS
THE ELEMENTS OF SUBGROUP II-B

BERYLLIUM, Be
MAGNESIUM, Mg

SUBGROUP A	SUBGROUP B
Calcium, Ca	Zinc, Zn
Strontium, Sr	Cadmium, Cd
Barium, Ba	Mercury, Mg
Radium, Ra	

BERYLLIUM AND MAGNESIUM

These elements are included in neither subgroup since they have properties that might put them in either one. Beryllium, known originally as glucinum, was discovered in 1798 by L. B. Vauquelin. It was isolated by Wöhler and Bussy in 1828, and was obtained in the pure form by Lebeau in 1898. The name glucinum was assigned to it because its soluble salts had a sweet taste. The name beryllium originated from the mineral beryl, which is the source of the element.

Magnesium was first isolated by Davy in 1808, and he obtained only a small amount of the element. His work on the isolation of sodium and potassium had just been completed and he was anxious to isolate the alkaline earth metals. After several disappointing attempts he was successful in forming mercury amalgams by the electrolysis of moist alkaline earths in contact with mercury. The mercury could be distilled and the free element obtained. Magnesium was not obtained in any quantity until 1831, when Bussy devised the procedure of heating magnesium chloride with potassium in a glass tube. The potassium chloride was removed by washing with water.

Magnesia nigra is a term that was used to designate the black oxide of manganese. Since a naturally occurring basic magnesium carbonate was white, it was designated as magnesia alba. This is given as the origin of the term magnesium for the metal, but the origin of the name magnesia is not definite.

Occurrence. The chief source of beryllium is a beryl which is the metasilicate of the element and aluminum, $(BeO)_3 \cdot Al_2O_3\text{-}(SiO_2)_6 \cdot 6H_2O$; it is comparatively scarce. Beryls containing a small amount of chromium silicate are known as emerald.

Magnesium is widely distributed in nature in the form of various minerals. Some of the more common ones are Epsom Salt ($MgSO_4 \cdot 7H_2O$), carnallite ($MgCl_2 \cdot KCl \cdot 6H_2O$), magnesite ($MgCO_3$), dolomite ($MgCO_3 \cdot CaCO_3$) and some mixed silicates such as Talc [$Mg_3H_2(SiO_3)_4$] and asbestos [$CaMg_2(SiO_3)_4$]. Magnesium ions are responsible, along with calcium ions, for the so-called "hardness" of water. These ions form insoluble salts with soap.

Epsom Salt, an important naturally occurring salt of magnesium, was so named because it was obtained from Epsom, Surrey (England). The springs are reported to have been found in 1618 and Epsom had become an important spa by the middle of the century. The bitter water had beneficial effects, both internally and externally. An artificial salt soon had to be prepared since the limited supply at Epsom could not meet the demand.

Methods of Formation and Preparation.

I. Dissociation of Halides.

$$M''X_2 \xrightarrow{\text{elect.}} M + X_2$$

$$MgCl_2 \xrightarrow{\text{elect.}} Mg + Cl_2$$

This method is the most important one in commercial use; the raw material is obtained from sea water. Beryllium is also prepared electrolytically.

II. Reduction of Binary Compounds.

A. $M''X_2 + 2Na \text{ (or K)} \rightarrow M + 2NaX(KX)$

$$MgCl_2 + 2K \rightarrow Mg + 2KCl$$

The present cost of magnesium would make this process of questionable value from a commercial standpoint. This is the historical method of Bussy.

B. $4M''O + Fe_2Si \text{ or (C)} \xrightarrow{\Delta} 4M + 2FeO + SiO_2$

$$4MgO + Fe_2Si \rightarrow 4Mg + 2FeO + SiO_2$$ [1]

This is known as the Pidgeon process and is a batch operation. It was used during World War II, but cannot compete, as to price, with the electrolytic procedure.

C. $MgO + C \xrightarrow{\Delta} Mg + CO$ [1]

The method is known as the Hansgirg process and is also a batch operation. There have been promising results in attempts to improve the carbothermic technique so that it could be used as a continuous process.

D. $BeO + Ca \xrightarrow{\Delta} Be + CaO$

Physical and Chemical Properties.

Table 38. Properties of Beryllium and Magnesium

Name	Beryllium	Magnesium
Density	1.85	1.74 [5]
Melting point (°C.)	1,350	651
Atomic number	4	12
Atomic weight	9.1	24.32

The metal beryllium is very hard as well as being ductile and malleable. It greatly increases the hardness of metals such as iron and copper when it is added to them.

Magnesium is a lustrous, silver-white metal; however, the luster is rapidly dulled upon exposure to the oxygen of the air because of the formation of a thin film of magnesium oxide. It is both malleable and ductile. Magnesium burns when heated and ignited, producing an intense white light and forming a white smoke of magnesium oxide according to the reaction

$$2Mg + O_2 \rightarrow 2MgO$$

The temperature of burning magnesium is reported to be 3,360° C.

Beryllium and magnesium have many similar chemical properties, but two important differences should be noted. Beryllium, in contrast to magnesium, does not react with nitric acid to form the nitrate and it is not soluble in aqueous solutions of the alkali hydroxides.

The carbonate of beryllium is soluble in water and is strongly hydrolyzed in solution. Magnesium carbonate, however, is only sparingly soluble in water.

The hydroxides of beryllium and magnesium are precipitated from aqueous solutions containing the respective ions by the addition of solutions of sodium or potassium hydroxide.

$$Be^{++} + 2NaOH \rightarrow Be(OH)_2 + 2Na^+$$

$$Mg^{++} + 2NaOH \rightarrow Mg(OH)_2 + 2Na^+$$

Milk of Magnesia, which is essentially a suspension of magnesium hydroxide in water, may be prepared by using a solution of magnesium sulfate and adding a sufficient quantity of sodium hydroxide in solution. Beryllium hydroxide is soluble in a slight excess of sodium hydroxide, but it is reprecipitated by boiling. Ammonium hydroxide may be used as a source of the hydroxyl ions, but the slight dissociation of NH_4OH results in an incomplete reaction; the addition of the NH_4Cl solution before the

NH_4OH is added prevents the formation of a precipitate. This is attributable to the common ion effect, which appreciably reduces the ionization of the NH_4OH.

The addition of disodium phosphate solution to a solution of a soluble beryllium or magnesium salt, in the presence of ammonium chloride, yields the corresponding beryllium or magnesium ammonium phosphate as an almost insoluble precipitate.

$$Mg^{++} + Na_2HPO_4 + NH_4Cl \rightarrow MgNH_4PO_4 + 2Na^+ + HCl$$

Ammonium chloride prevents the precipitation of the beryllium or magnesium hydroxide which would be formed as a consequence of the hydrolysis of the sodium phosphate. This is a commonly used test for the identification of magnesium ions.[2]

Uses.

INORGANIC BERYLLIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE. The compounds of beryllium are of no special value in pharmacy. It is significant, however, that workers exposed to beryllium compounds in some cases have developed a delayed chemical pneumonitis.[3] As mentioned elsewhere, beryllium is important in industry because it gives a longer life to springs for watches and other mechanical contrivances. Electric heating elements, fluorescent lamps and radio tubes are a few of the many additional examples of items using the element.

It has been reported that cuts caused by fluorescent bulbs coated with zinc berryllium silicate will produce peculiar cutaneous lesions unless they are widely excised.[4]

INORGANIC MAGNESIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

Magnesium had been used as a metal in comparatively small amounts until its usefulness was established in World War II, particularly because of its light weight. It has been shown to be especially valuable in alloys for structural uses. The Germans and the Allies made extensive use of metallic magnesium for incendiary bombs. It is also used in "flash bulbs" in photography and in pyrotechnics.

Magnesium is an essential element in both animal and plant life. It is in the chlorophyll of plants and is found in blood serum, where it is present to the extent of two to three mgm. per cent, a part of which is bound to protein. This element is also found in the cells of animal tissue, especially in muscle. Magnesium ions are very slowly absorbed through the intestinal walls. Thus, when magnesium salts are taken internally, they cause water to move into the bowel by osmosis, causing a cathartic action.

A wet pack made with a saturated solution of magnesium sulfate and applied externally will result in an osmotic flow of water from the tissues and probably will act as a

TABLE 39. INORGANIC MAGNESIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA	COMMON NAME
Magnesium Chloride	$MgCl_2$	....
Magnesium Bromide	$MgBr_2$	....
Magnesium Oxide	MgO	Magnesia, Light Magnesia
Heavy Magnesium Oxide	MgO	Heavy Magnesia
Magnesium Hydroxide	$Mg(OH)_2$	....
Magnesium Sulfate	$MgSO_4 \cdot 7H_2O$	Epsom Salt
Tribasic Magnesium Phosphate	$Mg_3(PO_4)_2 \cdot 5H_2O$	....
Magnesium Carbonate (U.S.P.)	$(MgCO_3)_4 \cdot Mg(OH)_2 \cdot 5H_2O$	Magnesia Alba
Magnesium Trisilicate	$(MgO)_2 \cdot (SiO_2) \cdot (H_2O)_n$	....
Talc (U.S.P.)—a naturally occurring hydrated magnesium silicate.		

local anesthetic. Thus, this treatment is often used for sprains, and is also said to give relief in erysipelas.

The magnesium ion, especially as magnesium sulfate, has a depressant action, affecting the central nervous system and the peripheral neuromuscular system. Magnesium sulfate has also been used as an anesthetic, being administered by injection.

THE ALKALINE EARTH METALS

The elements calcium, barium and strontium are known as the alkaline earth metals and have many very similar properties. Radium is also in subgroup II-A and has many properties of the alkaline earth metals, but since it is radioactive, it is described with those elements having that peculiar property.

Occurrence. As indicated by the term "alkaline earths," the elements of this subdivision are found widely distributed in the mineral kingdom. They only occur, however, in combination. Calcium compounds are widely distributed in the animal and plant kingdoms, barium compounds are found in some plants and strontium is apparently restricted to the mineral kingdom. Calcium is present in bones and teeth as tricalcium phosphate.

Important minerals which consist of almost pure calcium carbonate are chalk, limestone, marble and calcite; witherite is barium carbonate, and strontianite is strontium carbonate. Some other minerals also contain carbonates, either as mixed salts or as mixtures, e.g., dolomite, which consists of calcium carbonate and magnesium carbonate, and barytocalcite, which is a barium calcium carbonate.

Sulfates of these elements also are widely distributed; thus, gypsum ($CaSO_4 \cdot 2H_2O$), anhydrite ($CaSO_4$), barite or heavy spar ($BaSO_4$) and celestite (also called celestine [$SrSO_4$]), are commonly found. Many silicates also contain calcium, barium and strontium. Calcium is found as fluorspar (CaF_2) and as phosphate rock (Ca_3PO_4).

Methods of Formation and Preparation. The elements calcium, barium and strontium are of no special use in pharmacy; however, the reactions by which they are obtained are of interest.

Calcium may be obtained by the electrolysis of calcium chloride at temperatures kept below 800° C., according to the reaction:

$$CaCl_2 \text{ (fused)} \xrightarrow{\text{elect.}} Ca + Cl_2$$

Barium is obtained by reducing barium oxide with silicon, in the absence of oxygen, at about 1,200° C.

$$2BaO + Si \xrightarrow{\Delta} 2Ba + SiO_2$$

Strontium carbonate or sulfate is treated to produce strontium chloride. Strontium then is obtained by electrolysis of this fused salt.

Properties.

TABLE 40. PROPERTIES OF THE ALKALINE EARTH METALS

NAME	CALCIUM	STRONTIUM	BARIUM
Density	1.55	2.6	3.5^{20}
Melting point (°C.)	810	752 (800)	850
Atomic weight	40.08	87.63	137.36
Atomic number	20	38	56

The properties of all the alkaline earth metals are very similar. They will combine with oxygen and the halogens, but they do so readily only when heat is applied. Likewise, they react much less slowly with water than do the alkali metals, but they do form the hydroxides and liberate hydrogen. The resulting hydroxides can be converted to the oxides by heating; this is also applicable to the carbonates and the nitrates. On the other hand, the oxides unite very vigorously with water to form the hydroxides; in so doing

they liberate heat. The chemical addition or reaction of water with calcium oxide is known as "slaking," and temperatures as high as 150° C. can be attained in this process. The reaction between barium oxide and water is still more vigorous, and much higher temperatures may be obtained. Calcium Hydroxide U.S.P. is soluble in water in the amount of approximately 0.18 Gm. per 100 cc.; the hydroxides of barium and strontium are much more soluble, particularly in hot water.

The salts of the alkaline earth metals exhibit some interesting similarities. The chlorides and the sulfates are progressively less soluble with the increase in the atomic weight of the cation. Calcium sulfate is soluble to the extent of about 0.2 Gm. per 100 cc. of water at 20° C., whereas Barium Sulfate is soluble in the amount of only 0.0023 Gm. This solubility of calcium sulfate is responsible, in part, for the so-called "permanent" or "noncarbonate" hardness of water. The chlorides, nitrates and chlorates of the alkaline earths are water-soluble.

The slight solubility of many of these salts offer characteristic identity tests for their respective ions; for example, the formation of barium sulfate is the basis of the gravimetric assays for both soluble sulfates and soluble barium salts.

Calcium ions give a yellow-red color, barium ions give a yellowish-green color and strontium ions give a crimson color to a nonluminous flame.

Uses.

INORGANIC CALCIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

Calcium as an ion or salt is a very essential element in the body. It is of prime importance in the bony structures, the dry bones containing about 60 per cent calcium. It is also required for the normal clotting of blood. Calcium is found only in the extracellular fluid; normal serum contains about 10 mgm. per cent. The calcium ion is also necessary for the proper functioning of the autonomic and voluntary nervous systems. The average adult requires about 0.45 Gm. of calcium per day; growing children require more. Calcium deficiency results in numerous unpleasant symptoms, most of them being accompanied by nervous disturbances.

TABLE 41. INORGANIC CALCIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA	COMMON NAME
Calcium Chloride	$CaCl_2 \cdot 2H_2O$	...
Calcium Bromide	$CaBr_2$	...
Calcium Chloride-Hypochlorite	$CaOCl \cdot Cl \cdot H_2O$	Bleaching powder, chlorinated lime
Calcium Hydroxide	$Ca(OH)_2$	Slaked lime
Calcium Oxide	CaO	Quick lime
Calcium Sulfide	CaS	...
Calcium Sulfate	$CaSO_4 \cdot 2H_2O$	Gypsum
	$(CaSO_4)_2 \cdot H_2O$	Plaster of paris
Calcium Hypophosphite	$Ca(PH_2O_2)_2$	...
Calcium Phosphate, Tribasic	$Ca_3(PO_4)_2$	...
Calcium Phosphate, Dibasic	$CaHPO_4 \cdot 2H_2O$	...
Calcium Arsenate	$Ca_3(AsO_4)_2$	...
Calcium Carbonate, Precipitated	$CaCO_3$	Precipitated chalk
"Prepared Chalk"	$CaCO_3$ (97 per cent)	Drop chalk

Calcium salts * are widely used to supply the essential calcium ions. Precipitated calcium carbonate has the additional property of being an antacid when taken orally. Calcium Chloride produces an acid reaction and will reduce the pH of the blood; the calcium ion is deposited in bone or absorbed in the intestines, thus leaving the chloride ions free to combine with cations which are in combination with the bicarbonate of the blood. This causes a reduction of the bicarbonate and disrupts the bicarbonate-carbonic acid ratio, producing an acidosis. Calcium chloride also has a diuretic effect.

The calcium salts are used in the treatment of various forms of tetany, as an antispasmodic and for certain edemas.

INORGANIC BARIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

TABLE 42. INORGANIC BARIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA
Barium Chloride	$BaCl_2 \cdot 2H_2O$
Barium Peroxide	BaO_2
Barium Hydroxide	$Ba(OH)_2 \cdot 8H_2O$
Barium Sulfide	BaS
Barium Sulfate	$BaSO_4$
Barium Nitrate	$Ba(NO_3)_2$

The barium ion is very toxic. The only soluble barium salt used medicinally is Barium Chloride, which is employed in conditions of heart block.

Barium Sulfate † is an insoluble powder and is used as a contrast medium in roentgenography, especially in fluoroscopic work. Barium sulfide is used as a depilatory and also in certain white paints.

Barium Hydroxide T.S. is a saturated solution of barium hydroxide. It must be prepared by using carbon dioxide-free water and then must be carefully protected from carbon dioxide in order to prevent the precipitation of barium carbonate. It is used as a reagent.

THE INORGANIC STRONTIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

TABLE 43. INORGANIC STRONTIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA
Strontium Bromide	$SrBr_2 \cdot 6H_2O$
Strontium Nitrate	$Sr(NO_3)_2$

The strontium ion is comparable to the calcium ion, but it cannot replace the latter in the prevention and treatment of the symptoms of calcium deficiency. The idea that strontium salts were especially useful in relieving certain symptoms has not been substantiated by careful scientific investigations. Strontium salts are used for the effect of the anions, e.g., bromide and carbonate.

Strontium nitrate is also used as a source of strontium ions for making powders that burn with a red color in pyrotechnics.

THE ELEMENTS OF SUBGROUP II-B

Zinc was first recognized as a metal by Paracelcus in the sixteenth century. It had been used long before this, however, in the form of brass (a copper-zinc alloy).

Cadmium was recognized in the form of its oxide and isolated as a metal in 1817 by Strohmeyer. It was observed in zinc oxide, but the yellow color previously was thought to be arsenic.

Mercury was named after the messenger

* In addition to the inorganic salts listed in the table, calcium salts of organic acids are commonly known. Calcium Gluconate, Calcium Lactate and Calcium Mandelate are U.S.P. XIII salts of this type.

† It should always be remembered that abbreviations are never used for barium sulfate, barium sulfide and barium sulfite. The last two are somewhat soluble in the stomach and severe poisoning will result if they are used instead of barium sulfate.

of Jove since it rapidly disappeared upon the application of heat. The alchemist's symbol for mercury was the messenger's wand, which is also used to represent the planet Mercury. Mercury is commonly known as quicksilver, a name originally assigned to it because of its silvery appearance and characteristic properties as a liquid. It was known to the ancients, having been mentioned as early as 400 B.C. by Aristotle. Theophrastus (300 B.C.) described a method of obtaining it from its ore, cinnabar, and called it liquid silver. The name Hydrargyrum is derived from the two Greek names for water and silver and it is this name from which the modern symbol, Hg, is derived.

Occurrence. Zinc occurs chiefly as the sulfide in the ore commonly known as zinc blende. This ore is found, along with the lead ore (galena), in the tristate area of Oklahoma, Kansas and Missouri. Other zinc ores are zinc carbonate (smithsonite) and zinc silicate (willemite); less important ores are the sulfate, the oxide and a mixed oxide containing iron and manganese in addition to zinc. Zinc is produced in Spain, England, Belgium and other European areas, as well as in the states mentioned above; it also is produced in Wisconsin, Colorado, Idaho, Montana and New Jersey.

Cadmium is found in comparatively small percentages in many zinc ores, primarily as the sulfide. The mineral greenockite is largely cadmium sulfide.

Mercury is found only in the mineral kingdom. The most abundant form is the sulfide, HgS, which is known as cinnabar. It is found in California, Spain, Italy and to a lesser extent in other areas. Mercury is marketed in iron "flasks" which hold 75 lbs. (The European flasks hold 34.5 kilograms.) It is also available from distributors in 5 lb. earthenware jugs.

Methods of Formation and Preparation.

I. Formation of the Oxides from the Sulfides and the Subsequent Reduction to the Element.

$$2M''S + 3O_2 \xrightarrow{\Delta} 2M''O + 2SO_2$$

$$M''O + C \xrightarrow{\Delta} M + CO$$

A. $2ZnS + 3O_2 \xrightarrow{\Delta} 2ZnO + 2SO_2$

$$2ZnO + 2C \xrightarrow{\Delta} 2Zn + 2CO$$

B. $2CdS + 3O_2 \xrightarrow{\Delta} 2CdO + 2SO_2$

$$2CdO + 2C \xrightarrow{\Delta} 2Cd + 2CO$$

Zinc and cadmium are associated in the naturally occurring ore known as zinc blende. This ore is chiefly zinc sulfide, and the cadmium was generally lost through the flues until a few years ago. The ore is roasted, changing the sulfides to the oxides. The oxides then are reduced to the metals by heating with carbon in the form of coal. Since cadmium boils (see physical properties) at a lower temperature than zinc, it is removed first. The product contains some zinc and zinc oxide and it is converted to the sulfate with sulfuric acid; the cadmium is precipitated as the sulfide in acid solution. After further treatment, it is reconverted to the oxide and heated with charcoal.

After the cadmium has been removed, the temperature is increased and zinc is obtained. If the zinc is contaminated with other elements such as lead, iron, arsenic, sulfur, etc., it may be purified by electrolysis.

II. Reduction of Metallic Sulfides.

$$M''S + O_2 \xrightarrow{\Delta} M + SO_2$$

$$HgS + O_2 \xrightarrow{\Delta} Hg + SO_2$$

Mercury is obtained from its ore, which is known as cinnabar and is chiefly mercuric sulfide, by direct distillation without the need of the reducing action of carbon. If the oxide is produced at all, it is readily decomposed at the temperature used. Tin, lead, zinc, silver, etc., are frequently separated, as the last step in its purification, by distilling the mercury.

Properties.

TABLE 44. PROPERTIES OF THE ELEMENTS OF SUBGROUP II-B

	ZINC	CADMIUM	MERCURY
Density	7.14	8.64	13.54
Melting point (°C.)	419.4	320.9	−38.89
Boiling point (°C.)	907	767 ± 2	360
Atomic weight	65.38	112.4	200.6

There is an increase in density with an increase in atomic weight and a corresponding decrease in the melting and boiling points.

The chemical properties of the oxides and sulfides are very similar. However, mercury is below hydrogen in the activity series and there is a significant difference in the reaction of these elements with acids. Zinc and cadmium are attacked with dilute acids, except nitric acid, with the liberation of hydrogen. The reducing property of zinc is further illustrated by the fact that it reduces nitric acid to ammonium nitrate; mercury reacts with nitric acid to produce nitrogen tetroxide. (Mercurous nitrate is formed slowly with cold, dilute nitric acid and mercury, whereas concentrated nitric acid produces mercuric nitrate.)

$$4Zn + 10HNO_3 \rightarrow 4Zn(NO_3)_2 + NH_4NO_3 + 3H_2O$$

$$Hg + 4HNO_3 \xrightarrow[\text{low temp.}]{\text{(conc.)}} Hg(NO_3)_2 + N_2O_4 + 2H_2O$$

$$6Hg + 8HNO_3 \xrightarrow{\text{(dil.)}} 3Hg_2(NO_3)_2 + N_2O_2 + 4H_2O$$

Zinc will burn in the vapor state, but none of the elements of subgroup II-B react to any extent with oxygen at ordinary temperatures. This property is made use of in the coating of iron, usually by electroplating, with zinc and with cadmium to prevent rusting.

Mercury does not react with acids to form salts, except with nitric acid and concentrated sulfuric acid, so that mercury salts are usually prepared by the action of acids upon the oxide or by double decomposition. The oxides and sulfides of zinc, cadmium and mercury are insoluble in water. The hydroxides of zinc and cadmium are also insoluble; a hydroxide of mercury is not known. Zinc hydroxide not only reacts with acids but also reacts with bases to form soluble zinc salts, but the other two elements do not behave in this manner.

$$Zn(OH)_2 + 2H^+ \rightarrow Zn^{++} + 2H_2O$$

$$Zn(OH)_2 + 2(OH)^- \rightarrow (ZnO_2)^{--} + 2H_2O$$

Mercury forms both mercuric, $(Hg)^{++}$, and mercurous, $(Hg_2)^{++}$, compounds. The difference is thought to be a matter of difference in mass rather than a true variation of the active electron valency. Mercurous salts have properties that are similar to the properties of the silver salts. Mercurous chloride is an insoluble white powder; mercurous oxide is a black powder. Mercurous nitrate is soluble in water but is partially hydrolyzed by it. Mercuric salts may be reduced by mercury to form mercurous salts. Other reducing substances also reduce mercuric salts. Stannous chloride, for example, will reduce mercuric chloride to mercurous chloride, but when added in excess, it will completely reduce the mercury ions to mercury. Metallic utensils made of iron or tinned iron will react with mercuric chloride to reduce the mercuric ion to mercury; thus, mercuric chloride solutions must be made in nonmetal utensils.

Cadmium also forms cadmous compounds somewhat like mercury. Cadmium chloride is reduced to cadmous chloride when heated with cadmium. Cadmous chloride is hydrolyzed with water to form cadmous hydroxide $[Cd_2(OH)_2]$, which can be changed to the oxide by applying gentle heat.

Each of the three elements has the char-

acteristic property of forming complex ions. Zinc hydroxide will react as a weak acid. Ammonium hydroxide is a weak base. The two compounds, in the presence of water, form a water-soluble compound which has been shown to contain a complex ion, $Zn(NH_3)_4^{++}$. Cadmium hydroxide also reacts to form the complex ion $[Cd(NH_3)_4]^{++}$. Zinc and cadmium will form the complex $[Zn(CN)_4]^{++}$ and $[Cd(CN)_4]^{--}$ ions. Mercuric cyanide may be produced by the reaction between mercuric oxide and hydrocyanic acid; this compound then will react with alkali cyanides to form the $[Hg(CN)_4]^{--}$ ions.

Mercuric iodide is practically insoluble in water, but the addition of a soluble iodide, such as potassium iodide, causes the compound to go into solution. This is due to the formation of the complex ion $(HgI_4)^{--}$. Mercurous iodide, also water-insoluble, reacts with an excess of potassium iodide in solution to form free mercury and the mercuric salt, which is immediately changed to the $(HgI_4)^{--}$ ion. Cadmium halides, in concentrated solution, also form complex ions, e.g., $(CdCl_4)^{--}$; the salt is $Cd(CdCl_4)$.

Uses.

INORGANIC ZINC COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

The zinc ion has the property of reacting with proteins to form an insoluble precipitate. It is this characteristic that makes the zinc compounds useful as astringents. When applied in a concentrated form, they have escharotic properties. The zinc salts also exhibit some antiseptic action. Since zinc salts are very irritating, they are used almost entirely for external application; however, zinc sulfate has been used as an emetic. Zinc oxide, peroxide and calamine (also zinc carbonate) are insoluble in water and are commonly employed as aqueous suspensions; ointments, pastes and liniments are also very commonly used forms. Medicinal Zinc Peroxide has been used fre-

TABLE 45. INORGANIC ZINC COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA	CHARACTERISTICS
Zinc Chloride	$ZnCl_2$	Very deliquescent, forming a highly acidic and corrosive liquid
Zinc Iodide	ZnI_2	Very deliquescent and tends to liberate free iodine
Zinc Oxide	ZnO	Calamine * is ZnO with traces of ferric oxide; Prepared Neocalamine N.F. is prepared by mixing 3 Gm. of Red Ferric Oxide, 4 Gm. Yellow Oxide and 93 Gm. of Zinc Oxide
Zinc Peroxide	ZnO_2	Medicinal Zinc Peroxide U.S.P. contains not less than 45 per cent of ZnO_2 together with zinc carbonate and zinc hydroxide
Zinc Sulfide	ZnS	Only in White Lotion
Zinc Carbonate	$ZnCO_3$	Official in U.S.P. IX as Precipitated Zinc Carbonate with the approximate formula $(ZnCO_3)_2 \cdot [Zn(OH)_2]_3$
Zinc Permanganate	$Zn(MnO_4)_2$	....

* This is now the U.S.P. name. It was originally known as Prepared Calamine; Calamine was used, at that time, to designate an impure Zinc Carbonate which contained some ferric oxide.

quently as a 40 per cent creamy suspension in water to cover the surface of open wounds.

INORGANIC MERCURY COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

ized in aqueous solutions, producing an acid reaction. A saturated solution at 25° C. contains 7.4 grams in 100 cc., but the compound is commonly employed in concentrations of 1:2,000 and 1:1,000 as an antiseptic wash, a dressing and a sterilizing agent. One of the Large Bichloride Tablets N.F. will make 1 pint of a 1:1,000 solution; one of the Small Bichloride Tablets N.F. will make 4 fl. oz. of a 1:1,000 solution. The salt is obtained by heating mercuric sulfate and sodium chloride, by the action of hydrochloric acid on mercuric oxide or by the action of chlorine on mercury.

TABLE 46. INORGANIC MERCURY COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

NAME	FORMULA	COMMON NAME
MERCURIC COMPOUNDS		
Mercuric Chloride	$HgCl_2$	Bichloride of Mercury, Corrosive Sublimate, Corrosive Mercuric Chloride
Red Mercuric Iodide	HgI_2	Biniodide of Mercury
Ammoniated Mercury	$HgNH_2Cl$	White Precipitate
Yellow Mercuric Oxide	HgO	Yellow Precipitate (an impalpable powder)
Red Mercuric Oxide	HgO	Red Precipitate (a crystalline powder or crystalline scales)
Mercuric Sulfide	HgS	...
Mercuric Nitrate	$Hg(NO_3)_2$	...
Mercuric Cyanide	$Hg(CN)_2$	...
Mercuric Oxycyanide	$Hg(CN)_2HgO$	...
Potassium Mercuric Iodide	K_2HgI_4	...
MERCUROUS SALTS		
Mercurous Chloride	$HgCl$ or (Hg_2Cl_2)	Calomel; Subchloride of Mercury
Yellow Mercurous Iodide	HgI	Proto-iodide of Mercury
Mercurous Nitrate	$HgNO_3$	...

Elemental mercury has been used, especially in ointment form, as a parasiticide, and Mild Mercurial Ointment (Blue Ointment) is in the U.S.P. Strong Mercurial Ointment U.S.P. is used for the treatment of syphilis. Mercury with Chalk N.F. has some use as a laxative: Mercury Mass N.F. also has a similar use. Mercury is used in thermometers and barometers and in preparing amalgams for use in dentistry and in chemical reactions.

The mercuric ions react with proteins to form a precipitate. This reaction is the basis for the antiseptic properties of mercuric and the mercurous compounds. The readily soluble salts react very quickly and thus are very irritating.

Mercury Bichloride N.F. is a white, crystalline compound that is stable in air and in aqueous solution; it is only slightly ionized in aqueous solutions, producing an acid reaction.

Red Mercuric Iodide N.F. is a bright-red, amorphous powder. It is changed to a yellow modification by heating (127° C.), but this yellow powder rapidly reverts to the red color upon cooling. Red Mercuric Iodide is not soluble in water but it is readily dissolved in aqueous solutions of alkali iodides or sodium thiosulfate. A solution may be prepared very easily by triturating 1 mol of HgI_2 with slightly more

than 2 mols of KI and adding water; the compound formed is K_2HgI_4. The latter salt, mercuric potassium iodide, is described in the N.N.R.;[5] it is said to be useful for the same purposes that Mercuric Iodide and Mercuric Chloride are applicable, but it has the advantage of being more soluble than the former and safer than the latter.

Ammoniated Mercury U.S.P. is a white, water-insoluble, amorphous powder or it may be obtained as small irregular pieces. Chemically, it is amminomercuric chloride or mercurammonium chloride and has the formula $HgNH_2Cl$. The compound must be protected from light since it turns black upon exposure. It is soluble in aqueous solutions of sodium thiosulfate, with the evolution of ammonia; when it is heated, a precipitate of red mercuric sulfide separates. The compound is used for skin diseases and as a parasiticide, usually as the U.S.P. 5 per cent ointment. Ammoniated Mercury is prepared by adding an aqueous mercuric chloride solution to a solution of ammonia with constant stirring.

$$HgCl_2 + 2NH_4OH \rightarrow HgNH_2Cl + NH_4Cl + H_2O$$

Yellow Mercuric Oxide U.S.P. is a water-insoluble compound that is precipitated when solutions containing mercuric ions are added to solutions of hydroxyl ions, e.g.,

$$Hg(NO_3)_2 + 2NaOH \rightarrow HgO + 2NaNO_3 + H_2O$$

Red Mercuric Oxide N.F. is the residue obtained by carefully heating mercuric nitrate or by heating mercury in an atmosphere of oxygen at approximately 350° C. (It does not react at lower temperatures, and mercuric oxide is decomposed at higher temperatures.)

Mercuric sulfide is a black powder that may be obtained by the interaction between mercuric salts and soluble sulfides, both in slightly acid solution.

$$HgCl_2 + H_2S \rightarrow HgS + 2HCl$$

This is the basis for the U.S.P. test for mercuric ions in solutions.

The compound is readily soluble in aqua regia and in solutions of alkali sulfides, where it forms the ion $(HgS_2)^{--}$. When the black mercuric sulfide is heated carefully enough to prevent decomposition, it is converted to a red product known as vermilion which is used in printer's ink, etc.

Mercuric Nitrate is contained in N.F. Mercuric Nitrate Ointment, which contains from 6.65 per cent to 7.35 per cent of mercury in combination. Mercuric nitrate is obtained when an excess of nitric acid is added to mercury.

$$3Hg + 8HNO_3 \rightarrow 3Hg(NO_3)_2 + N_2O_2 + 4H_2O$$

The crystalline compound has the formula $Hg(NO_3)_2 \cdot 8H_2O$. Mercuric nitrate is used for somewhat the same purposes as is mercuric chloride, but it is more of an irritant because of its greater degree of ionization in solution.

Mercuric Cyanide N.F. is a colorless or white crystalline substance; it is also available as a white powder. It is soluble in water, 1 Gm. in 13 cc., forming a neutral solution. The compound is used in 1:1,000 and 1:2,000 concentrations as an antiseptic. It may be given internally by intravenous or intramuscular injection in 10 mgm. daily doses.

Mercuric Oxycyanide N.N.R. is a white microcrystalline powder that is used as an antiseptic in 1:5,000 solutions. One gram is soluble in 80 cc. of water. It has certain advantages over mercuric chloride; it does not react with metallic instruments and it does not act on albumin to as great a degree, so that it is less irritating.

Mild Mercurous Chloride U.S.P., Calomel, is a heavy white powder that is practically insoluble in water and other common solvents. The compound is subject to oxidation and reduction by the action of light, forming mercuric chloride and some

free mercury. Calomel or calomel tablets that have been exposed to light will usually assume a gray color or will have black spots scattered over the surface; this suggests probable oxidation and the product should be discarded. Mercurous chloride also may be oxidized by oxidizing agents, and care must be taken to avoid such reactions when calomel is used internally. The compound is a laxative when taken internally and is a parasiticide when used externally (usually as a dust or an ointment).

The salt is prepared by the interaction between mercurous ions and chloride ions, both in solution, e.g.,

$$2NaCl + Hg_2(NO_3)_2 \rightarrow 2HgCl + 2HNO_3$$

Yellow Mercurous Iodide N.F. is a yellowish-orange powder. It turns black on the surface when exposed to light; this is caused by decomposition. Mercurous iodide is insoluble, or practically so, in water, alcohol and ether. The compound will react with ammonia or alkali hydroxides, forming mercurous oxides or possibly some free mercury. Mercurous iodide will also react in the presence of an excess of an alkali iodide, in solution, to form mercuric iodide and free mercury. The compound may be prepared, however, by the careful addition of a dilute solution of potassium or sodium iodide to a solution of mercurous nitrate.

Mercurous Nitrate is a water-soluble compound (p. 179). It is prepared easily at room temperature by the action of dilute nitric acid on mercury. The dihydrate, $Hg_2(NO_3)_2 \cdot 2H_2O$, is a white to colorless crystalline compound that is easily oxidized to a basic mercuric nitrate, $Hg(OH)NO_3$, in the presence of water and air. This basic salt is a yellow compound that is not soluble in water. The presence of a slight amount of nitric acid in water will prevent the precipitation of the basic compound and the hydrolysis of mercurous nitrate, but the mercurous salt is oxidized very readily and care must be taken to minimize the exposure of the salt to oxygen.

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16

Elements of Group I

THE ALKALI METALS
THE ALKALI HYDROXIDES
THE METALS OF SUBGROUP I-B

Lithium, Li
Sodium, Na

Subgroup A	Subgroup B
Potassium, K	Copper, Cu
Rubidium, Rb	Silver, Ag
Cesium, Cs	Gold, Au

THE ALKALI METALS

The elements lithium, sodium and potassium, together with rubidium and cesium, form the class of elements commonly known as the alkali metals. The elements of this class possess one electron in the outer shell; they lose this electron with ease, thus, they are strongly electropositive, cesium being the most electropositive and lithium the least electropositive. The elements and their salts produce characteristic, colored flames. Ammonia, while not a metal, forms salts that are very similar, in many ways, to the alkali salts; therefore, these salts are studied together.

The term alkali was originally used to describe the soluble salt obtained from the ashes of plants. Earlier forms of the word were the Arabic *alqili* (ashes of saltwort), the old French *alcali* and the Middle English *alkaly* and *alcaly*. The term caustic alkali still is commonly used to designate the hydroxides of the alkali metals, while the term mild alkali (the carbonates) has become obsolete. Another old terminology that is retained in a limited way is that of the fixed alkalies and the volatile alkalies, the latter referring to the hydroxide and the carbonate of ammonia. The most important early use of the "alkalies" or ashes, especially of those from seaweed, was in the preparation of soap. Soap manufacture still requires alkalies, but they are obtained by industrial methods.

The alkali metals were first obtained in the free state in 1807 by Sir Humphry Davy, who prepared both potassium and sodium by electrolysis of the hydroxides. A short time later Gay-Lussac and Thenard reported a method by which they could obtain sodium by the reduction of caustic soda and potassium by the reduction of caustic potash, using molten iron as the reducing agent. These two metals were originally thought to be oxides, but this concept was disproved by Gay-Lussac and Thenard.

Lithium was discovered by Arfvedson in 1817. The name was derived from the Greek word *lithos,* meaning stone, and it was so named because it was thought to be found only in stone.

Cesium was discovered by Bunsen and Kirchhoff, by the use of the spectroscope, in 1860. It was isolated in 1881 by Setterberg.

Rubidium was discovered by Bunsen and Kirchhoff, also with the spectroscope.

Ammonia is the trihydride of nitrogen (p. 154) but it has the chemical characteristic of adding a proton, i.e., a hydrogen ion, to become the ammonium ion $(NH_4)^+$. Crude ammonium chloride was obtained by sublimation from the ashes of camels' dung by the Egyptians. In this form it was known

as Sal Ammoniac, and this term is used today as a synonym for the official salt. Since the salts of ammonia have many analogous physical properties and ammonium hydroxide commonly is referred to as a volatile alkali, it is appropriate to study the ammonium compounds here.

Occurrence. The chemical activity of the alkali metals is such that they do not occur free in nature. Sodium and potassium are abundant in the form of salts, lithium is rare and the distribution of rubidium and cesium is very limited. Sodium chloride is found in the ocean and in salt lakes, e.g., in the Great Salt Lake in Utah and in the Dead Sea. It is also found in salt wells and underground deposits, a few of which are found in Michigan, New York and Germany. Sodium nitrate, known as Chile saltpeter, is found in Chile. A form of sodium pyroborate, $Na_2B_4O_7 \cdot 4H_2O$, is found in California, while the decahydrate, $Na_2B_4O_7 \cdot 10H_2O$, is found in Tibet and is known as tincal. There are also limited amounts of the sulfate and carbonate.

Potassium occurs as the chloride, chiefly as carnallite, which has the formula $KCl \cdot MgCl_2 \cdot 6H_2O$. It is also found as kainite, which is a mineral with the formula $K_2SO_4 \cdot MgSO_4 \cdot MgCl_2 \cdot 6H_2O$. Deposits of these minerals are found in Germany, Poland, Spain and the United States, particularly in California and New Mexico.

Lithium is found in some mixed silicates of which lepidolite (lithium aluminosilicate) is an important example. Lithium aluminum fluorophosphate, which is known as amblygonite, is another source. The element is also present in small amounts with some naturally occurring phosphates and silicates of sodium and potassium. The important sources of lithium are California, New Mexico, Arizona, South Dakota, Canada, France and Saxony.

Rubidium is found in small amounts in lepidolite and also with potassium chloride in the Stassfurt mines. Cesium occurs as aluminosilicates, particularly pollucite, in Maine, South Dakota and the island of Elba; it also is found with lepidolite.

Ammonia is formed by the decomposition of protein materials under certain conditions. The original source of ammonium chloride has already been mentioned. Ammonia originally was prepared by heating the horns and hoofs of animals and it was known as Spirits of Hartshorn.

Sodium ions are found in the extracellular fluids of the animal body, thus, sodium ions are present in blood serum. Potassium ions, on the other hand, are found in the intracellular fluids of the body; these ions are present in the red blood corpuscles. Sodium and potassium salts are also present in plants. For example, potassium nitrate is widely distributed and is found in the tobacco plant in amounts as high as ten per cent in the dried plant.

Methods of Formation and Preparation.

I. Electrolysis of the Chlorides or Hydroxides.

A. $2M'X \xrightarrow{\text{elect.}} 2M + X_2$

$$2NaCl \xrightarrow[\text{fused}]{\text{elect.}} 2Na + Cl_2$$

The electrolytic production of the alkali metals, especially sodium and potassium, is by far the most important method in commercial use. The addition of electrolytes that are less reactive to hydrolysis than sodium chloride served to lower the melting point from about 800° C. down to 600° C. and made this a practical method.

B. $4M'OH \xrightarrow{\text{elect.}} 2M + H_2 + O_2$

$$2KOH \xrightarrow{\text{elect.}} 2K + H_2 + O_2$$

The hydroxides have lower melting points than the chlorides and therefore are reactive at lower temperatures. This method of electrolysis is known as the Castner method and is less important commercially than it was formerly.

II. Reduction of Anhydrous Chlorides by Heating with Calcium.

$$2M'X + Ca \xrightarrow{\Delta} 2M + CaX_2$$

$$2NaCl + Ca \xrightarrow{\Delta} 2Na + CaCl_2$$

III. Reduction of the Oxides by Heating with Carbon. (This is not applicable to lithium.)

$$M'_2O + C \xrightarrow{\Delta} 2M + CO$$

(Fe, Al or Mg may also be used as reducing agents.)

IV. For Methods of Preparing Ammonia, see page 155.

Properties.

Table 47. Properties of the Alkali Metals

	Li	Na	K	Rb	Cs
Melting point (°C.)	186	97.5	62.3	38.5	28.5
Boiling point (°C.)	1609 ± 5°	880	760	700	670
Density	0.534	0.97	$0.86^{20°C.}$	1.53	1.9
Atomic number	3	11	19	37	55
Atomic weight	6.939	22.997	39.095	85.48	132.91
Isotopes (at. wt.)	6, 7	23	39, 40, 41	85, 87	133

Because of their comparatively low melting points, these metals are soft and easily are cut with a knife or even a spatula at ordinary temperatures. When freshly cut, they exhibit a silver, metallic luster but this is rapidly dulled to a whitish color because of rapid oxidation; the coating consists of a mixture of the hydroxide, the oxide and the carbonate.

The alkali metals are soluble in mercury, forming the well-known mercury alkali amalgams, for example, sodium amalgam, which are useful as reducing agents and for various other purposes.

The most characteristic chemical property of this group of elements is their strong electropositive character. Thus, they readily combine with oxygen in the air. This property makes it essential to store the elements in an inert medium such as mineral oil or kerosene. Sodium is shipped in special hermetically sealed metallic cans from which the air has been removed. The strong affinity for oxygen is also demonstrated by the vigorous reaction of the elements when they come in contact with water, the reaction liberating hydrogen. The heat of this reaction often results in the ignition of the hydrogen; since the hydrogen becomes mixed with the oxygen in air, explosions frequently result. This property of liberating hydrogen is indicative of the strong reducing character of the alkali metals.

Alkali metals form many compounds which are, with the exception of some lithium salts, rather freely soluble in water. The oxides react with water, forming water-soluble hydroxides. These hydroxides, with the exception of lithium hydroxide, are deliquescent. In the solid state, the hydroxides exist as crystalline masses which are normally available as sticks, small pellets or flakes. The aqueous solutions are strongly alkaline and are very caustic when brought in contact with tissues such as the skin. The solids and their solutions, upon exposure to air, absorb carbon dioxide very rapidly.

The alkali metals combine directly with elements other than oxygen to form compounds. They unite with the halogens to form halides, M'X (p. 54), with sulfur to form sulfides, M'_2S (p. 100), with nitrogen to form nitrides, Li_3N and with hydrogen to form hydrides, M'H.* They also unite with

* Sodium hydride (NaH) [1] is particularly useful as a powerful reducing agent. It is formed by the action

other elements; in these compounds the alkali metals form monovalent cations. They may also form covalent ($NaCH_3$) and chelate compounds.

The salts of the alkali metals in which the anion is from a strong acid, e.g., the sulfates and halides, form neutral aqueous solutions. Salts of weaker acids tend to hydrolyze and form alkaline solutions. Thus sodium carbonate, sodium bicarbonate, sodium monohydrogen phosphate, Sodium Borate U.S.P., potassium acetate and other similar salts produce alkaline solutions in water, the reaction

$$Na_2CO_3 + H_2O \rightleftharpoons NaOH + NaHCO_3$$

being a specific illustration of the hydrolysis reaction.

The strongly basic characteristics of the alkali metals makes possible the formation of acid salts, as illustrated by the bicarbonates, bisulfates, bisulfites, acid phosphates, etc. They also react with such hydroxides as bismuth trihydroxide, an amphoteric compound, to form bismuthites.

The ammonium ion is similar to the alkali metallic ions in that its salts behave like the alkali salts. Its hydroxide is a weak base, however, and the ammonium ion is not very stable.

Uses.

Inorganic Compounds of the Alkali Metals of Pharmaceutical Importance. The salts of the alkali metals have already been discussed under the various anions, such as the chlorides, nitrates, carbonates and other compounds. At this time, it is of interest to summarize them and to correlate the properties that are attributed to the respective metallic ions.

THE ALKALI HYDROXIDES

As mentioned under the alkali metals, a very characteristic chemical property is their strong affinity for oxygen. They react with water to form the respective water-soluble hydroxides. The alkali hydroxides are very strongly basic. These properties are made the basis for their uses, especially of sodium and potassium hydroxides. Typical reactions of the alkali hydroxides are represented by the following reactions, in which M′ represents any one of the alkali metallic ions.

1. $M'OH + H^+ \rightarrow H_2O + M^+$

This is the general reaction of acidimetry and alkalimetry as illustrated in the various applications of the volumetric and test solutions of NaOH and KOH in the U.S.P. and the N.F. Sodium hydroxide and potassium hydroxide absorb CO_2 from the air to form carbonates. A similar reaction takes place with the amphoteric hydroxides, e.g.,

$$NaOH + AlH_3 \rightarrow NaAlO_2 + 2H_2O$$

2. $2M'OH + M^{++}\ (\text{or } M^{+++}) \rightarrow M''(OH)_2 + 2M^+$

This reaction will take place whenever $M''(OH)_2$ is insoluble. Thus, milk of magnesia may be prepared by adding magnesium sulfate to sodium hydroxide in aqueous solution. Ferric hydroxide is precipitated when a solution of ferric chloride is made alkaline with a solution of sodium or potassium hydroxide.

3. $2M'OH + 2\ \text{Metal} + 2H_2O \rightarrow 2M'M'''O_2 + 3H_2$

Aluminum reacts with the alkali hydroxides in aqueous solution to form the compound $M'AlO_2$. Zinc reacts with fused sodium hydroxide to form Na_2ZnO_2. Even platinum is affected by fused alkali hydroxides.

4. $M'OH + X_2 \rightarrow NaX + NaOX + H_2O$

Chlorine, bromine and iodine will react with aqueous solutions of the alkali hydroxides (p. 57). The alkali hydroxides also

of hydrogen on sodium at about 360°. The compound reacts with water to form hydrogen and sodium hydroxide. Lithium aluminum hydride [2] is another useful reducing agent.

react with other nonmetals. For example, phosphorus reacts with sodium hydroxide, as shown by the reaction:

$$3NaOH + 4P + 3H_2O \rightarrow 3NaPH_2O_2 + PH_3$$

Methods of Formation and Preparation.

I. ACTION OF WATER ON ALKALI METALS.

$$2M + 2HOH \rightarrow 2M'OH + H_2$$

A. $2Na + 2HOH \rightarrow 2NaOH + H_2$

B. $2K + 2HOH \rightarrow 2KOH + H_2$

Commercially, this reaction is the second one to take place in the electrolysis of sodium chloride or potassium chloride. Chlorine is obtained as one of the products of electrolysis and the alkali metal is the other. The alkali metal then reacts with water to produce the corresponding hydroxide. The two products must be kept separate to prevent interaction between them to form chlorine compounds, the simplest reaction being:

$$NaOH + Cl_2 \rightarrow NaCl + NaOCl + H_2O$$

(See p. 57 for further discussion.)

The electrodes are separated either by an asbestos diaphragm or by a mercury cell. In the latter case, the alkali metal forms an amalgam with the mercury cathode; the amalgam is then run into a cell containing water, where the alkali hydroxide is formed.

II. ACTION OF CALCIUM HYDROXIDE ON AN ALKALI CARBONATE.

$$M'_2CO_3 + Ca(OH)_2 \rightarrow 2M'OH + CaCO_3$$

$$Na_2CO_3 + Ca(OH)_2 \rightarrow 2NaOH + CaCO_3$$

$$K_2CO_3 + Ca(OH)_2 \rightarrow 2KOH + CaCO_3$$

$$(NH_4)_2CO_3 + Ca(OH)_2 \rightarrow NH_4OH + CaCO_3 \rightleftharpoons NH_3 + H_2O$$

This process is gradually being replaced by the electrolytic process above. Hydrated lime [$Ca(OH)_2$] is mixed with soda ash (Na_2CO_3) and then added to water. The mixture is filtered, and the residue is washed with water to remove all of the alkali hydroxide.

The alkali hydroxide solutions above, which contain from about 8 per cent up to 50 per cent of the compound, may be evaporated to dryness in iron kettles. The material may then be formed into flakes, sticks or pellets, or it may be crushed.

III. ACTION OF WATER (HYDROLYSIS) ON ALKALI SALT OF A WEAK ACID.

$$M'_2 \text{ salt of weak acid} + HOH \rightleftharpoons 2M'OH + \text{Weak Acid}$$

$$Na_2CO_3 + HOH \rightleftharpoons 2NaOH + H_2CO_3$$

$$K_2CO_3 + HOH \rightleftharpoons 2KOH + H_2CO_3$$

$$Na_2B_4O_7 + 7HOH \rightleftharpoons 2NaOH + 4H_3BO_3$$

$$Na_3PO_4 + H_2O \rightleftharpoons NaOH + Na_2HPO_4$$

When alkali salts of weak acids are dissolved in water, an alkaline solution results. This is due to hydrolysis, and the degree of alkalinity is dependent upon both the equilibrium which is established and the concentration of the salt. Obviously, this type of reaction cannot be used to prepare the alkali hydroxides but it is very important in the use of such solutions. The resultant alkalinity is responsible for many hydrolysis reactions.

The Official Alkali Hydroxides.

Sodium Hydroxide U.S.P. (Caustic Soda) must not contain more than 3 per cent of Na_2CO_3, which is calculated together with the NaOH as total alkali; the U.S.P. requires not less than 95 per cent total alkali. The compound is very deliquescent and absorbs carbon dioxide from the air. These properties make it essential that Sodium Hydroxide be kept in tight containers.

One gram of Sodium Hydroxide is soluble in 1 cc. of water. It is freely soluble in alcohol. Its solutions are very caustic and will destroy skin, other organic tissues, certain fabrics, etc. Sodium Hydroxide is known as caustic soda. Aqueous solutions of Sodium Hydroxide are used, in varying concentrations, as volumetric and test solutions.

The compound also is used in the manufacture of soap, in petroleum refining and in many other ways.

Soda Lime U.S.P. is a mixture of sodium hydroxide or potassium hydroxide (or both) with calcium hydroxide. It is used, as indicated by the U.S.P., for the absorption of carbon dioxide in metabolism tests, oxygen therapy and anesthesia. Soda Lime must be kept in tight containers.

Potassium Hydroxide U.S.P. (Caustic Potash) is permitted to contain as much as 3.5 per cent of K_2CO_3. It must contain a minimum of 85 per cent of total alkali, which is calculated as KOH. This compound is very deliquescent and absorbs carbon dioxide from the air, making it necessary to store it in tight containers.

One gram of Potassium Hydroxide is soluble in 1 cc. of water, in 3 cc. of alcohol and in 2.5 cc. of glycerin. In addition to the aqueous volumetric and test solutions, there are alcoholic solutions of potassium hydroxide that are half-normal and tenth-normal. The 0.5 N alcoholic solution is used in certain assays, e.g., Glyceryl Triacetate, in the tests for chemical constants in fats and oils and in other similar ways.

Strong Ammonia Solution U.S.P. (Stronger Ammonia Water) contains an equivalent of from 27 per cent to 29 per cent of NH_3. The probable equilibrium that exists in the solution is represented by the following reaction between ammonia and water.

$$NH_3 + H_2O \rightleftharpoons NH_4OH \rightleftharpoons (NH_4)^+ + (OH)^-$$

The amount of NH_4OH is exceedingly small in comparison to the amount of NH_3 in solution.

Diluted Ammonia Solution U.S.P. (Ammonia Water) contains an equivalent of from 9 to 10 Gm. of ammonia in each 100 cc. of solution.

LITHIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

TABLE 48. INORGANIC LITHIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA
Lithium Bromide N.F.	LiBr
Lithium Carbonate N.F.	Li_2CO_3

The lithium ion may be identified by the flame test. In this, the lithium salt is moistened with hydrochloric acid and placed in a nonluminous flame; a crimson color is observed. Solutions of lithium salts, when made alkaline with sodium hydroxide solution, will produce a white precipitate of lithium carbonate upon the addition of Sodium Carbonate T.S. The precipitate is soluble in ammonium chloride solution. Thus, the only general reaction of the lithium ion, that of interionic reaction, is illustrated. This reaction is regulated by the solubility of the carbonate in water (1:100).

The lithium ion is said to have a diuretic action, and some lithium salts have been used for this effect. It is also reported to have a depressant action on circulation. Continued usage of lithium compounds tends to produce a gastro-enteritis.

SODIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

The sodium ion may be identified by the flame test in which the sodium salt produces a yellow color when placed in a nonluminous flame. Sodium chloride or sodium nitrate will produce a golden-yellow precipitate upon the addition of cobalturanyl acetate T.S. The formula for this precipitate is usually given as $NaC_2H_3O_2 \cdot Co(C_2H_3O_2) \cdot 3UO_2(C_2H_3O_2)_2$.[3] Other bivalent metals, such as zinc or magnesium, may be used to replace the cobalt. The sodium ion has no specific action upon body tissues; however, sodium salts do cause nausea when taken orally in sufficient amounts. Sodium is important, however, since it is limited entirely to extracellular fluids and therefore plays a

TABLE 49. INORGANIC SODIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA	COMMON NAME
Sodium Chloride U.S.P.	$NaCl$	Salt
Sodium Bromide U.S.P.	$NaBr$	....
Sodium Iodide U.S.P.	NaI	....
Sodium Fluoride	NaF	....
Sodium Hypochlorite	$NaOCl$ (in solution only, e.g., Sodium Hypochlorite Solution, U.S.P.)	....
Sodium Sulfate U.S.P.	$Na_2SO_4 \cdot 10H_2O$	Glauber's Salt
Sodium Sulfite, Exsiccated, U.S.P.	Na_2SO_3	....
Sodium Hydroxide U.S.P.	$NaOH$	Caustic Soda
Sodium Dichromate	$Na_2Cr_2O_7 \cdot 2H_2O$	....
Sodium Peroxide N.N.R.	Na_2O_2	....
Sodium Thiocyanate N.F.	$NaSCN$	Sodium Rhodanate
Sodium Thiosulfate U.S.P.	$Na_2S_2O_3 \cdot 5H_2O$	Sodium Hyposulfite, Hypo
Sodium Nitrate	$NaNO_3$	Chile Saltpeter
Sodium Nitrite U.S.P.	$NaNO_2$	....
Sodium Phosphate, Tribasic	$Na_3PO_4 \cdot 12H_2O$	....
Sodium Phosphate U.S.P.	$Na_2HPO_4 \cdot 7H_2O$	....
Sodium Biphosphate U.S.P.	$NaH_2PO_4 \cdot H_2O$	....
Sodium Metaphosphate	$NaPO_3$ [also as polymers $(NaPO_3)_x$]	....
Tetrasodium Pyrophosphate	$Na_4P_2O_7 \cdot 10H_2O$	TSPP
Sodium Hypophosphite	$NaH_2PO_2 \cdot H_2O$	....
Sodium Arsenate, Exsiccated, N.F.	Na_2HAsO_4	....
Sodium Carbonate, Monohydrate, U.S.P.	$Na_2CO_3 \cdot H_2O$	....
Sodium Carbonate, Anhydrous	Na_2CO_3	Commercial form is Soda Ash
Sodium Carbonate, Decahydrate	$Na_2CO_3 \cdot 10H_2O$	Sal Soda, Washing Soda
Sodium Sesquicarbonate	$Na_2CO_3 \cdot NaHCO_3 \cdot 2H_2O$	....
Sodium Silicate	Na_2SiO_3	30 per cent solution known as Water Glass
Sodium Borate U.S.P.	$Na_2B_4O_7 \cdot 10H_2O$	Borax, Sodium Tetraborate
Sodium Perborate U.S.P.	$NaBO_3 \cdot 4H_2O$ (or $NaBO_2 \cdot H_2O_2 \cdot 3H_2O$)	....

definite role in regulating the amount of these fluids by an osmotic effect. This is a most interesting subject and more can be found about it in textbooks on pharmacology.

POTASSIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE.

The potassium ion will produce a violet color when any potassium compound is placed in a nonluminous flame. The color is masked when sodium ions are also present, but the sodium flame may be filtered by the use of "cobalt glass." Potassium salts in solutions made acid with acetic acid form a golden-yellow precipitate of dipotassium cobalt nitrate according to the reaction

$$2K^+ + Na_3Co(NO_2)_6 \xrightarrow[H^+]{HOH} K_2NaCo(NO_2)_6 \cdot H_2O + 2Na^+$$

The potassium ion is present in intracellular fluid and is considered to be the specific cation in the cell. It is present in sufficient concentration to establish an osmotic equilibrium between the fluid within the cell and that which surrounds it. The potassium may

TABLE 50. INORGANIC POTASSIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

Compound	Formula	Common Name
Potassium Permanganate U.S.P.	$KMnO_4$	Permanganate of Potash
Potassium Chloride U.S.P.	KCl	....
Potassium Bromide U.S.P.	KBr	....
Potassium Iodide U.S.P.	KI	....
Potassium Chlorate N.F.	KO_3Cl	....
Potassium Perchlorate, U.S.P. Reagent	KO_4Cl	....
Potassium Bromate, U.S.P. Reagent	KO_3Br	....
Potassium Iodate, U.S.P. Reagent	KO_3I	....
Potassium Hydroxide U.S.P.	KOH	Caustic Potash
Potassium Polysulfides (Sulfurated Potash N.F.)	A mixture of K_2S_x and $K_2S_2O_3$	....
Potassium Bisulfate, U.S.P. Reagent	$KHSO_4$	....
Potassium Sulfate	K_2SO_4	....
Potassium Chromate, U.S.P. Reagent	K_2CrO_4	....
Potassium Dichromate, U.S.P. Reagent	$K_2Cr_2O_7$	....
Potassium Nitrate N.F.	KNO_3	Saltpeter
Potassium Nitrite, U.S.P. Reagent	KNO_2	....
Potassium Hypophosphite N.F.	KH_2PO_2	....
Potassium Phosphate, Monobasic, U.S.P. Reagent	KH_2PO_4	....
Potassium Thiocyanate N.F.	$KSCN$	Potassium Rhodanate, Potassium Sulfocyanate
Potassium Cyanide, U.S.P. Reagent	KCN	....
Potassium Carbonate U.S.P.	$K_2CO_3 \cdot 1\frac{1}{2}H_2O$	Salt of Tartar
Potassium Bicarbonate U.S.P.	$KHCO_3$	....
Potassium Ferricyanide, U.S.P. Reagent	$K_3Fe(CN)_6$	....
Potassium Ferrocyanide, U.S.P. Reagent	$K_4Fe(CN)_6 \cdot 3H_2O$	....
Potassium Aluminum Sulfate U.S.P.	$KAl(SO_4)_2 \cdot 12H_2O$	Alum

diffuse through the cell wall, and a small concentration of potassium is normally present in extracellular fluids. Most potassium salts are administered for the effect of the anion; however, the action of potassium nitrate or potassium chloride is reported to be that of the potassium ion. Potassium salts are diuretic due to the rapid elimination of the cation by the kidneys, this action being due to the somewhat rigid capacity of the body, or balance, for potassium ions.[4]

AMMONIUM SALTS OF PHARMACEUTICAL IMPORTANCE.

The ammonium ion is identified by the addition of sodium hydroxide or potassium hydroxide to an ammonium salt. Ammonia is evolved and it may be recognized by its characteristic odor. Ammonia may also be identified by the action of the gas, or vapors from a solution, upon moistened red litmus paper, which is changed to blue.

Ammonium salts, especially the chloride, have an expectorant action. The carbonate, which is alkaline, is also used for this purpose. These salts stimulate secretions of mucus and are used primarily in the form of "cough" syrups.

The ammonium salts have a diuretic effect that may be explained by the production of an acid reaction in the body. The ammonium ion is changed to urea. The anion is thus free and will cause the bicarbonate ion $(HCO_3)^-$ to lose the H^+. This results in a lowering of the bicarbonate concentration and disrupts the balance between this ion and the carbonate in the body.

The body may also form the ammonium ion from urea. This reaction takes place in

TABLE 51. INORGANIC AMMONIUM COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA	COMMON NAME
Ammonium Chloride U.S.P.	NH_4Cl	Sal Ammoniac; Muriate of Ammonia
Ammonium Bromide N.F.	NH_4Br	....
Ammonium Iodide N.F.	NH_4I	....
Ammonium Hydroxide U.S.P.	NH_4OH	Only as Strong Ammonia and Diluted Ammonia Solution U.S.P.
Ammonium Sulfide	$(NH_4)_2S$	Only as Ammonium Sulfide T.S., U.S.P.
Ammonium Polysulfide	$(NH_4)_2S_x$	Only as Ammonium Polysulfide T.S., U.S.P.
Ammonium Sulfate	$(NH_4)_2SO_4$	....
Ammonium Aluminum Sulfate	$NH_4Al(SO_4)_2 \cdot 12H_2O$	Ammonium Alum
Ammonium Nitrate	NH_4NO_3	....
Ammonium Thiocyanate	NH_4SCN	....
Ammonium Reineckate	$NH_4[Cr(NH_3)_2(SCN)_4] \cdot H_2O$	Reinecke Salt
Ammonium Phosphate Dibasic	$(NH_4)_2HPO_4$	....
Ammonium Hypophosphite	$NH_4H_2PO_2$	....
Ammonium Carbonate U.S.P.	$NH_4HCO_3 \cdot NH_4NH_2CO_2$	Sal Volatile
Ammonium Vanadate	NH_4VO_3	Ammonium Metavanadate

the renal cells and the ammonium ion thus is made available to neutralize excess acid. The ammonium salt is eliminated in the urine. It is in this manner that the ammonium ion is important in regulating the acid-base equilibrium of the body.

Ammonia, when inhaled, acts as a stimulant. It affects the respiratory and vasomotor centers. When inhaled in high concentrations, ammonia is very irritating to the nose, throat and lungs. It also irritates the eyes. For example, when Strong Ammonia Solution is being handled, the operations should be performed in a well-ventilated hood or in the open. Such solutions not only give off high concentrations of ammonia, but also are very irritating to the skin if they come into contact with it.

THE METALS OF SUBGROUP I-B

The elements of subgroup I-B, copper, silver and gold, have many properties that are in direct contrast to those of the alkali metals (the elements of subgroup I-A). Some relationship is demonstrated by the fact that the elements of both subgroups form compounds in which they are monovalent. They differ in that the elements of subgroup I-B form other compounds in which their valences are higher; this is especially true of copper and gold.

The date for the discovery of copper is prehistoric since it was probably the first metal that was used by man. The Latin name for copper is *cuprum,* from which the symbol Cu is derived.

Silver also dates back to ancient civilization, where it was used for making ornaments and coins. The Latin name for silver is *argentum,* from which the symbol Ag is derived. The word silver originated with the Anglo-Saxon term *seolfor*. Since silver is a white, shining metal, the term *Luna* was assigned to it and it was represented by the crescent moon in the writings of the alchemists.

Gold jewelry, ornaments and coins have been found in the archeological studies of all early civilizations. It is still very widely

used for these purposes. The physical properties of gold, especially its color and malleability, make the metal particularly desirable for such uses. Its chemical nonreactivity also precludes tarnishing as well as other undesirable reactions. Pure gold is known as 24 karat. The amount of gold in alloys is indicated by numbers, e.g., 14 karat is interpreted to mean that it is 14/24 gold. The Latin name for gold is *aurum*, from which the symbol Au is derived.

Gold, together with silver, platinum and palladium, are known as the noble metals since they do not react readily with the common acids. Gold has long been used as a symbol of purity.

Occurrence. All of the metals of this subgroup occur free and in combination in nature. Copper is found in the free state in comparatively large deposits, especially in the Lake Superior region. It is more widely distributed in combination, being considered as an essential trace element for both plants and animals by many authorities. Important naturally occurring compounds of copper are $CuFeS_2$ (known as chalcopyrite), Cu_2S (chalcocite), a basic copper carbonate, $CuCO_3 \cdot Cu(OH)_2$, (Malachite) and Cu_2O (cuprite or red copper). The first two compounds are the most important and are found in Utah, Montana and Arizona in the United States, and in England, Germany and Spain. Gold and silver are found primarily in the uncombined state, but are also found, in limited amounts, in combination, especially in the form of sulfides and of certain alloys. Gold is also found in certain alluvial sands and in the oceans. Gold and silver are mined in the United States, especially in Colorado. The stories of the gold rushes to California and to Alaska are well known.

Methods of Formation and Preparation.

As previously mentioned, copper, silver and gold are found in the uncombined condition. It is necessary to separate the free metal from the gangue (adhering mineral material); this may be done by mechanical methods or more completely by chemical reactions. These processes are described in textbooks and other references on metallurgy. Copper is obtained from its ores, which consist mostly of the sulfide and oxide, by a series of steps which may be represented by the reactions:

$$2Cu_2S + 3O_2 \rightarrow 2Cu_2O + 2SO_2$$
$$2Cu_2O + Cu_2S \rightarrow 6Cu + SO_2$$

The copper obtained by this extraction is not sufficiently pure for many uses; therefore, it is purified further, usually by electrolysis.

The silver sulfide, found in some ores, produces silver sulfate when roasted under specified conditions. Silver is precipitated from a solution by the addition of copper. The reactions involved are:

$$Ag_2S + 2O_2 \rightarrow Ag_2SO_4$$
$$Ag_2SO_4 + Cu \rightarrow 2Ag + CuSO_4$$

Silver may be separated from lead, with which it is sometimes found, by the use of zinc. The zinc is mixed with the molten metals, the silver dissolves in it and is carried to the top. The zinc then is removed by heating. Silver, when it occurs in the free state in ores, may be removed by mixing the ore intimately with mercury which forms an amalgam. The mercury is then removed by distillation.

Both silver and gold may be obtained by the cyanide process. In this process the ore is treated with sodium cyanide and the gold in the cyanide is replaced by zinc or by some other reagent. The reactions for gold are essentially:

$$4Au + 8NaCN + O_2\ (\text{air}) + 2H_2O \rightarrow 4NaAu(CN)_2 + 4NaOH$$

$$4NaAu(CN)_2 + 2Zn \rightarrow 2Na_2Zn(CN)_4 + 4Au$$

Properties.

TABLE 52. PROPERTIES OF THE ELEMENTS OF SUBGROUP I-B

	Cu	Ag	Au
Melting point (°C.).......	1,085	960.5	1,062
Density (20° C.)	8.92	10.5	19.3
Atomic volume.	7.12	10.29	10.23
Atomic weight.	63.57	107.88	197.2

It should be noted that the melting points of these metals are much higher than those of the alkali metals. They are rather soft, however, being malleable as well as ductile. They are good conductors of electricity. There is no uniformity of color; ordinary copper is described as being "copper-colored," which is a reddish shade by reflected light, silver is "silver-white" and gold is yellow. In the colloidal state, various colors may be exhibited by these metals.

The metals of the copper group are comparatively inert, in significant contrast to the activity of the alkali metals. Their affinity for oxygen, for example, decreases with the increase in atomic weight. This property is demonstrated by the action of glucose (a reducing sugar); cuprous oxide is produced from an alkaline cupric solution,* but metallic silver and gold are obtained from solutions of their respective salts. Gold is precipitated from its solutions by the action of ferrous sulfate in solution, while silver can be precipitated only under certain special conditions and copper is not reduced to the metallic state. The reaction of ferrous sulfate with auric salts is the basis for a gold assay by which the gold is weighed as the metal, the reaction being written ionically as

$$Au^{+++} + 3Fe^{++} \rightarrow Au + 3Fe^{+++}$$

Copper, silver and gold are below hydrogen in the activity series and thus they will not displace hydrogen from acids. They will not react, for example, with hydrochloric acid. The reactions of copper with nitric acid and with sulfuric acid are based upon the power of these acids as oxidizing agents. The oxidation product of copper is converted to the corresponding salt by more of the acid. The specific reaction depends upon the temperature and concentration at which the reaction takes place. Cold dilute nitric acid reacts with copper according to the reaction

$$3Cu + 8HNO_3 \rightarrow 3Cu(NO_3)_2 + 2NO + 4H_2O$$

Concentrated nitric acid reacts as follows:

$$Cu + 4HNO_3 \rightarrow Cu(NO_3)_2 + 2NO_2 + 2H_2O$$

Silver also will form silver nitrate ($AgNO_3$) with nitric acid, but gold is nonreactive with all acids with the exception of the somewhat complex mixture that is known under the common name of aqua regia. This reagent is also known as Nitrohydrochloric Acid N.F., and its reaction with gold results in the formation of the stable, complex ion $AuCl_4^-$, which yields $HAuCl_4$ upon careful evaporation to dryness.

The atomic structures of the three elements in subgroup I-B have only one electron in their outer orbits, as would be expected. They would normally produce ions having a plus one charge, and many of their compounds show this to be true. This is not their only valence, however. Cuprous (Cu^+) compounds are well-known, but the cupric (Cu^{++}) compounds are more common. Aurous (Au^+) compounds are well-known, but auric (Au^{+++}) compounds are very

* Fehling's Solution and Benedict's Solution are examples of this type of solution and are used for both qualitative and quantitative estimation of glucose and other reducing sugars. The tests depend upon the formation of cuprous oxide.

frequently prepared. It is reported by Gibson [5] that gold exists in aurous compounds only as 2-covalent and in auric compounds only as 4-covalent. Silver forms the monovalent silver compounds almost exclusively, but the divalent compound AgO has been reported.

An important characteristic of the metals of this subgroup is the ease with which they form complex ions. This is somewhat characteristic of all subgroups as contrasted with the main groups. A common illustration of complex ion formation is the reaction of the respective ions with ammonia, forming the metal ammonium ion. Thus,

$$Cu^{++} + 4NH_3 \rightarrow Cu(NH_3)_4{}^{++}$$

and

$$Ag^{+} + 2NH_3 \rightarrow Ag(NH_3)_2{}^{+}$$

Some other illustrations are the $Ag(CN)_2{}^{-}$, $(CuBr_4)^{--}$ and $(AuCl_4)^{-}$ ions.

Uses.

INORGANIC COMPOUNDS OF THE ELEMENTS OF SUBGROUP I-B OF PHARMACEUTICAL IMPORTANCE.

The inorganic compounds of copper, silver and gold have already been described under the various anions. They are summarized here and the properties due to the respective cations are reviewed.

TABLE 53. INORGANIC COPPER COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA
CUPROUS COMPOUNDS	
Cuprous Chloride	$CuCl$
Cuprous Iodide	CuI
Cuprous Oxide	Cu_2O
CUPRIC COMPOUNDS	
Cupric Oxide	CuO
Cupric Hydroxide	$Cu(OH)_2$
Cupric Sulfate	$CuSO_4 \cdot 5H_2O$
Cupric Carbonate, basic	$Cu(OH)_2 \cdot CuCO_3$

The cuprous compounds, as a group, are practically insoluble in water. Most of the compounds are white, but Cu_2S is black and CuI is red. Cuprous chloride is hydrolyzed when an excess of water is added; it is soluble in hydrochloric acid, forming the compound $HCuCl_2$, or, with an excess of HCl, the compound H_2CuCl_3 or $(CuCl \cdot 2HCl)$. An important use of the hydrochloric acid solution is in the analysis of gases for carbon monoxide; the carbon monoxide is absorbed by the solution to form a white compound $(CuCl)_2CO$ or $CuClCO \cdot 2H_2O$.

Cuprous iodide is a red, water-insoluble powder. It is produced by the reaction between the cupric ion and soluble iodides in water solution. In acid solution, the following reaction takes place:

$$2Cu^{++} + 4I^{-} \rightarrow 2CuI + I_2$$

This is the basis of the U.S.P. assay for Cupric Sulfate.[6]

Cupric salts are usually white or yellow when anhydrous, but in the normal, hydrated state, the compounds are blue or blue-green. The cupric ion reacts with an excess of ammonia to form the deep-blue cupric-ammonium ion $Cu(NH_3)_4{}^{++}$, this being a common test for the cupric ion. Another common test for the cupric ion is dependent upon the fact that metallic copper is deposited on the surface of iron when it is introduced into a hydrochloric acid solution containing cupric ions. Cupric ions will also react with Potassium Ferrocyanide T.S. to produce a red precipitate of cupric ferrocyanide which is insoluble in dilute acids.

Cupric salts are widely used as fungicides. Cupric sulfate has been used, for example, in the treatment of epidermophytosis. Soluble cupric salts are irritant and astringent. When such solutions are taken internally, an emetic action is produced; however, they are toxic in smaller doses than are required to produce this effect. For use as a fungicide on plants, the practically insoluble cupric hydroxide is produced by mixing an aqueous suspension of calcium hydroxide with an aqueous solution of cupric sulfate. Cupric sulfate is also used in water

reservoirs and lakes for destroying algae and other plant growths.

Cupric oxide is a black compound that is commonly employed as an oxidizing agent in ultimate organic analysis.

TABLE 54. INORGANIC SILVER COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA
Silver Chloride, Colloidal	AgCl (10 per cent plus colloid stabilizing agent)
Silver Bromide..........	AgBr
Silver Iodide, Colloidal...	AgI (18 to 22 per cent plus gelatin as a colloid stabilizing agent)
Silver Oxide............	Ag_2O
Silver Sulfate............	$AgSO_4$
Silver Nitrate............	$AgNO_3$

The silver ion is normally monovalent. The silver halides and oxides are practically insoluble in water. Silver chloride is soluble in ammonium hydroxide, the resulting solution containing $Ag(NH_3)_2{}^+$ ions. Silver Nitrate is soluble in water to the extent of one gram in 0.4 cc. at 25° C. A precipitate will result upon the addition of chloride, bromide or iodide ions to an aqueous solution of Silver Nitrate ($AgNO_3$). Sulfide, arsenate, arsenite, sulfate, phosphate, carbonate and hydroxyl ions will also react to form insoluble or slightly soluble silver salts.

The silver ion precipitates protein, and this property is a characteristic of silver nitrate solutions. This compound and its modification (U.S.P. Toughened Silver Nitrate or U.S.P. Lunar Caustic), which contains not less than 94.5 per cent $AgNO_3$ and about 5 per cent AgCl, are used as caustics, astringents, antiseptics and germicides. Solutions containing from 0.1 to 10 per cent of silver nitrate are commonly used by local application, producing an immediate precipitation of a silver protein complex and resulting in a caustic effect. The precipitate may redissolve slowly, and the slowly liberated silver ions have a definite antiseptic action. When this effect is undesirable, one of the protein silver or colloidal silver halides can be used.

A condition known as argyria may develop when silver preparations are used for a long time. This is described as a deposit of silver in the skin.

TABLE 55. INORGANIC GOLD COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA
AUROUS COMPOUNDS	
Gold and Sodium Thiosulfate	$Na_3Au(S_2O_3)_2 \cdot 2H_2O$
AURIC COMPOUNDS	
Gold Chloride.............	$HAuCl_4 \cdot 4H_2O$ (Chlorauric acid)
Gold Bromide.............	$AuBr_3$

The auric ion reacts with Sodium Hydroxide T.S. to give a brown precipitate which is redissolved in an excess of the reagent. Stannous Chloride T.S. will produce a purple precipitate which is known as Purple of Cassius. The auric salts, such as auric chloride or auric bromide, are used in the preparation of gold salts of organic compounds, especially the thio compounds. The aurous compounds are always the result of this reaction. This reduction from the auric to the aurous ion is illustrated by the inorganic gold and sodium thiosulfate which may be prepared by the reaction between auric chloride and sodium thiosulfate.

Gold Chloride T.S., prepared by dissolving 1 Gm. of gold chloride in 35 cc. of water, is used as a reagent for the identification of certain alkaloids. Characteristic crystalline addition products are precipitated, e.g., the identity test for Atropine U.S.P.

Attempts have been made to use gold and its preparations for the treatment of various

diseases. Gold is very toxic and must therefore be used with utmost caution. When given by injection, a small per cent of the total gold is stored in the kidneys, with some going to the liver and the skin. The portion not stored is excreted.

Gold preparations, particularly those of organic compounds, are used with some success in the treatment of lupus erythematosus and rheumatoid arthritis. An elixir of gold bromide has a limited use in whooping cough.

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17

Elements of Group VIII

THE IRON GROUP	THE PLATINUM GROUP	
Iron, Fe	Ruthenium, Ru	Osmium, Os
Cobalt, Co	Rhodium, Rh	Iridium, Ir
Nickel, Ni	Palladium, Pd	Platinum, Pt

The elements of group VIII are known as transition * elements. The "iron group" consists of three transition elements in the first period of 18 elements. They have certain related properties (p. 7) which justify grouping them together. It will be observed that when arranged by atomic numbers, the elements are in the order listed above even though the atomic weight of cobalt is greater than that of nickel.†

The remainder of the elements of group VIII are commonly referred to as the platinum group of metals since they are associated together in nature and have similar physical and chemical properties.

THE IRON GROUP

An abundance of iron ores and the comparatively simple procedure by which iron was separated from them was the basis for an era in history that is known as the Iron Age. The influence of steel on the economy of the world, particularly of the United States, during the first half of the twentieth century can hardly be estimated at this time.

It is probable that the earliest people to make wrought iron were the Hindus of India. The Greeks are known to have produced a high-grade steel. The Latin name for iron is *ferrum,* from which the symbol Fe is derived.

Cobalt was first isolated by Brandt in 1735. The name is derived from the German *Kobold,* which referred to an underground spirit, so-called by miners since its presence in iron ores caused them trouble in separating the iron.

Nickel derived its name from the German *Kupfernickel,* a term that was applied to a nickel ore (NiAs). This ore closely resembled certain others that were rich in copper, but did not yield copper when smelted. An impure nickel was isolated by Cronstedt in 1751.

Occurrence. Iron is widely distributed in nature, being found in the mineral, animal and plant kingdoms. Meteorites contain iron in the metallic state, but the element is normally found in combination. Iron is very widely distributed in the mineral kingdom, being found in soils and water in varying amounts. Important iron ore deposits are found in Minnesota and Michigan; these ores are the red oxide known as hematite (Fe_2O_3). The iron ore deposits of the Adirondack region of New York are now commercially important, and certain others will become increasingly so. Another important ore, known as magnetite (Fe_3O_4), is mined in Norway, Sweden and, to a much lesser extent, in the eastern United States. Limonite ($2Fe_2O_3 \cdot 3H_2O$) is found in Germany and France, while iron stone ($FeCO_3$ mixed with clay and shale) is mined in Britain. Iron pyrites is widely distributed

* Transition elements are those elements which may lose electrons from the two outer energy levels.

† See physical properties, page 266.

and has been roasted to secure sulfur dioxide for use in making sulfuric acid; however, it has not been profitable to separate the iron from the oxidized materials.

Iron is essential in the animal kingdom as a constituent of the hemoglobin in blood. It is also found in the chromatin of the nucleus and is generally thought to be required for the reactions of oxidase enzymes.

Since iron is widely distributed in soils, it is to be expected that it is present in plants. Many plants or parts of plants that are utilized for food contain iron either in combination with nucleoproteins or as heme compounds; the elements may also be present as the ferrous ion. Fruits, green vegetables and some grains, especially wheat, are fairly high in iron content. It has been estimated that the amount of iron required by humans varies from about 5 mg. per day, as a minimum for an adult male, to approximately 20 mg. per day for a pregnant woman. The average daily diet is said to furnish from 10 to 20 mg. of iron.

Cobalt is found in the mineral kingdom in combination as simple and mixed arsenides, sulfarsenides and oxides; sulfides and an arsenate are also known. Some of the best-known ores are cobalt glance [$(CoFeAs)S_2$], speiss-cobalt [$(CoNiFe)As_2$], smaltite ($CoAs_2$), cobaltite ($CoAsS$), linneaite (Co_3S_4) and erythrite ($Co_3As_2O_7 \cdot 8H_2O$). Cobalt is primarily obtained as a by-product from the copper ores from the Belgian Congo and from the silver ores in Ontario.

The need for a trace amount of cobalt in the animal body has been demonstrated with sheep [1] and cattle.[2] This information establishes the fact that cobalt is present in soils and in plants, particularly in the grasses which normally furnish the animals with their requirements. The presence of 4 per cent cobalt in vitamin B_{12}, an anti-anemia factor, has given further evidence as to the significance of traces of this element in nutrition and in the treatment of anemia and related diseases.[3]

Nickel is found in the mineral kingdom. It is present in meteorites both as the free element and as an alloy with iron, the amount of nickel varying from 3 to 9 per cent. Pentlandite is an important source of this element; it is an ore containing nickel, copper and iron as sulfides. Chalcopyrite and pyrrhotite are similar ores. They are found principally in Ontario. Another important ore is a silicate of nickel and magnesium. It is found in New Caledonia and is known as garnierite.

Methods of Formation and Preparation.

I. Reduction of Metallic Oxides with Suitable Reducing Agents.

$$M'''_2O_3 + 3C \xrightarrow{\Delta} 2M + 3CO$$

A. $Fe_2O_3 + 3C \xrightarrow{\Delta} 2Fe + 3CO$

B. $Fe_2O_3 + 3CO \xrightarrow{\Delta} 2Fe + 3CO_2$

The reactions illustrated above are employed in the common commercial production of iron. The iron ore is mixed with coke and limestone and heated in a blast furnace. The complete process is best described in textbooks on metallurgy. Iron produced by this procedure is known as pig iron or cast iron and contains from 6 to 8 per cent of impurities such as carbon, silicon, manganese, phosphorus and sulfur. The melting point varies between 1,150° and 1,250° C. and it has a specific gravity of about 7.1.

When the impurities are removed so that the iron is from 99.8 to 99.9 per cent pure, the product is referred to as wrought iron. The specific gravity of this form of iron is about 7.7; it melts at about 1,500° C., but it begins to soften somewhat at about 1,000° C.

Steel is a name applied to iron which is almost free from other elements except carbon or, in some instances, other metals. The carbon content may be varied, and the type of steel is determined by the per cent of this element. Some steel may also contain other metals. Stainless steel, for example, is an

alloy of iron with 12 to 27 per cent chromium; some alloys contain nickel in an amount corresponding to 6.5 per cent or more.

C. $Fe_2O_3 + 3H_2 \xrightarrow{\Delta} 2Fe + 3H_2O$

This reaction takes place in the preparation of Reduced Iron N.F. It does not go to completion, but the official product must contain at least 90 per cent of iron. Iron by Hydrogen is a synonym for Reduced Iron.

D. $Co_3O_4 + 4CO \xrightarrow{\Delta} Co + 4CO_2$

Cobalt oxide and cobalt chloride can be reduced with carbon monoxide or with hydrogen.

E. $3Fe_3O_4 + 8Al \xrightarrow{\Delta} 9Fe + 4Al_2O_3$

This process is known as the Goldschmidt process. A mixture of magnetic iron oxide (76 per cent) and aluminum is known as thermite; the reaction between the two ingredients is strongly exothermic after it is initiated at a temperaure of about 1,800° C. Thermite was used during the early part of World War II as an incendiary; it also has been used for welding purposes. The Goldschmidt process is also employed in the commercial production of cobalt.

II. Oxidation of Metallic Sulfides.

$$M''S + O_2 \xrightarrow{\Delta} M + SO_2$$

$$NiS + O_2 \xrightarrow{\Delta} Ni + SO_2$$

Pentlandite, an ore of nickel which also contains copper and iron as sulfides, is heated in a furnace and finally "Bessemerized" to produce Monel metal. This is an alloy of copper (30 per cent) and nickel (60 per cent), a small amount of iron and a trace of aluminum. (This alloy is used particularly for sheet metal because it is not corroded by acids.)

III. Electrolysis of Metallic Halides.

$$M''Cl_2 \xrightarrow{\text{elect.}} M + Cl_2$$

$$NiCl_2 \xrightarrow{\text{elect.}} Ni + Cl_2$$

The nickel may be separated from the alloy obtained from the Bessemer furnace (II above) by the Browne electrolytic method. The final reaction is the electrolysis of nickel chloride.

Physical and Chemical Properties.

Table 56. Properties of the Metals of the Iron Group

	Iron	Cobalt	Nickel
Density	7.86	8.9	8.9
Melting point (°C.)	1,535	1,480	1,452
Atomic weight	55.85	58.94	58.69
Atomic number	26	27	28
Atomic volume	7.12	6.7	6.67
Election distribution	(K) 2-8-14-2	(K) 2-8-15-2	(K) 2-8-16-2

The elements iron, cobalt and nickel are the transition elements of the periodic table which link the element manganese in subgroup VII-A with copper in subgroup I-B in the first of the long periods having 18 elements. These elements, together with the elements having a similar position in the next two succeeding long periods, make up group VIII of the periodic table.

It may be observed from Table 56 that the physical properties of iron, cobalt and nickel are very similar. Cobalt and nickel have properties that are more nearly the

same, and this similarity is also found in their chemical properties.

At one time, it was thought that iron, cobalt and nickel were the only magnetic metals. This was due to the fact that this property was more pronounced in them than in other elements. Iron is, however, appreciably more magnetic than either cobalt or nickel.

A very pronounced chemical property of iron is its tendency to rust (oxidize to $3Fe_2O_3 \cdot H_2O$) upon exposure to moist air. Cobalt and nickel, however, will only combine with oxygen when heated. When heated iron comes into contact with steam, the oxide, Fe_3O_4, is formed; under the same conditions cobalt and nickel form the monoxides. (The rates of oxidation, as well as other chemical changes, are increased as the size of the metallic particles decrease.)

Iron, cobalt and nickel react with dilute acids to form the corresponding salts of bivalent metallic ions, with the liberation of hydrogen. Ferrous salts are green in the hydrated form, e.g., green vitriol ($FeSO_4 \cdot 7H_2O$); hydrated nickelous salts are a bright green. Hydrated cobaltous salts are, in contrast, a pink to red. Anhydrous ferrous salts, except FeS, are white, while anhydrous nickelous salts are yellow and anhydrous cobaltous salts are blue or sometimes green.

The "-ous" salts of these elements may be formed by the action of acids upon the corresponding oxides, hydroxides and carbonates.

The ferrous salts are very easily oxidized to the ferric salts; in the latter the iron is in the trivalent state. This oxidation is illustrated in the preparation of ferrous iodide for use in Ferrous Iodide Syrup; difficulty attributable to the formation of the ferric salt is frequently experienced.* When the ferrous compounds are oxidized without additional acid, basic salts[4] are produced. These salts are converted to the normal salt by the addition of more acid. Ferric salts, in which the valence of iron is 3+, are also produced by the action of an acid upon ferric oxide or ferric hydroxide and by the action of strong oxidizing agents, such as chlorine, directly upon iron.

Trivalent cobaltic or nickelic compounds are not commonly encountered in pharmacy. Nickelous and cobaltous compounds (divalent) are stable in air and in solution; however, cobaltous hydroxide may be oxidized to cobaltic hydroxide by strong oxidizing agents. Cobaltous compounds may also be oxidized when there are some additional ions which will form stable complex cobaltic ions, e.g., $K_3Co(NO_2)_6$ is produced when cobaltous salts are mixed with potassium nitrite and acetic acid. The only known nickelic compounds are the oxide and the hydroxide.

From the position of the elements in the periodic table, it might be expected that octavalent compounds could be prepared from iron, cobalt and nickel, as well as from the other elements in group VIII. Iron carbonyls have been prepared; one of these has the formula $Fe(CO)_4$. The corresponding nickel and cobalt carbonyls have also been prepared, but it is generally believed that these compounds do not represent octavalent positive elements but rather a co-ordinate type of valence. The elements osmium and ruthenium are known to produce the tetroxides OsO_4 and RuO_4, but the octavalence of the elements in group VIII is very uncommon.

Iron in both the ferrous and ferric valency states forms complex ions with cyanides and thiocyanates.

The complex ions are used as a colorimetric means for the identification of iron salts. The following is a typical reaction:

$$Fe^{+++} + 6CNS^- \rightarrow [Fe(CNS)_6]^{---}$$

Ferric chloride, for example, will react with potassium thiocyanate to produce a charac-

* The assays of ferrous iron preparations, using $KMnO_4$, $K_2Cr_2O_7$ and $Ce(SO_4)_2$, are based upon the oxidation of ferrous ions to the ferric state (p. 96).

teristic deep-red color due to the complex ion.

Other complex ions containing iron are the ferrocyanide $[Fe(CN)_6]^{----}$ and the ferricyanide $[Fe(CN)_6]^{---}$; they are used in the form of their potassium salts. Potassium ferrocyanide is produced by the reaction between ferrous sulfate and an excess of potassium cyanide in aqueous solution. The ferrocyanide may be oxidized to the ferricyanide by the action of chlorine according to the reaction:

$$2K_4[Fe(CN)_6] + Cl_2 \rightarrow 2K_3[Fe(CN)_6] + 2KCl$$

The U.S.P. describes potassium ferrocyanide, which contains three molecules of water of hydration, as transparent yellow crystals. Potassium ferricyanide occurs as dark-red crystals. Both salts are very soluble in water and insoluble in alcohol.

When potassium ferricyanide is added to a solution containing ferrous ions, e.g., $FeSO_4$, the following reaction takes place:

$$2K_3[Fe(CN)_6] + 3FeSO_4 \rightarrow Fe_3[Fe(CN)_6]_2 + K_2SO_4$$

Ferrous ferricyanide is known as Turnbull's blue and the reaction in which it is formed is a characteristic test for the ferrous ion.[5]

The addition of a solution containing ferric ions, e.g., ferric chloride, to a solution of potassium ferrocyanide produces a characteristic intense blue compound which is formed according to the reaction:

$$3K_4[Fe(CN)_6] + 4FeCl_3 \rightarrow Fe_4[Fe(CN)_6]_3 + 12KCl$$

Ferric ferrocyanide is known as Prussian blue.[5]

Reference has already been made to the cobaltic nitrite complex ion $[Co(NO_2)_6]^{---}$. Other cobaltic complexes are known, especially the cobaltamines. When ammonium hydroxide is added to an aqueous solution of cobaltous chloride and ammonium chloride and a stream of air is passed through the solution for several hours, a deep purple color is produced. The addition of hydrochloric acid precipitates a compound known as chloropentamine cobalt chloride having the formula $[Co(NH_3)_5Cl] \cdot Cl_2$. If a large amount of ammonium chloride is present, luteocobalt chloride is formed; this is a brownish-yellow compound and its formula is $Co(NH_3)_6Cl_3$.

Like the ferrous and ferric ions, the corresponding cobalt ions form the complex cyanide ions, i.e., $[Co(CN)_6]^{++++}$ and $[Co(CN)_6]^{+++}$. Complex nickelous ions, such as $[Ni(NH_3)_4]^{++}$ and $[Ni(NH_3)_6]^{++}$, are known, but the nickelic ion is not known to enter into such complexes.

Uses.

It is a well-established fact that iron deficiencies can be treated successfully by the administration of iron in the form of reduced iron, ferrous salts and ferric salts.* It is now generally thought that inorganic compounds are just as efficacious as the organic salts. There is some evidence that ferrous sulfate is the form from which the most iron is utilized, but this does not imply that it always should be the iron salt of choice. If the patient cannot tolerate a specific iron dosage or is not obtaining the proper response, other preparations, such as ferrous carbonate, Blaud's Pills and Vallet's Mass, may offer a satisfactory solution.

Iron, Quinine and Strychnine Elixir N.F., commonly known as Elixir of I. Q. and S., is a bitter tonic in which the iron is added in the form of Ferric Citrochloride Tincture. Ferric Chloride Solution and Sodium Citrate are mixed, and the complex salt,

* It has been thought, by some during the last 30 years, that iron was more readily assimilated when it was in organic combination. Thus, Ferric Ammonium Citrate U.S.P., Green Ferric Ammonium Citrate N.F., Ferrous Gluconate N.F., Ferrous Lactate N.N.R., Iron and Ammonium Acetate Solution N.F. and Ferric Citrochloride Tincture N.F. have received some acceptance.

TABLE 57. IRON AND ITS INORGANIC COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA	COMMON NAME
Iron N.F.	Fe	"Card Teeth"
Reduced Iron	Fe (90 per cent)	Iron-by-hydrogen, Quevenne's Iron
FERROUS COMPOUNDS		
Ferrous Chloride	$FeCl_2$	....
Ferrous Iodide	FeI_2	....
Ferrous Sulfide	FeS	....
Ferrous Sulfate	$FeSO_4 \cdot 7H_2O$	Green Vitriol, Copperas
Ferrous Carbonate	$FeCO_3$	....
FERRIC COMPOUNDS		
Ferric Chloride	$FeCl_3 \cdot 6H_2O$	Iron Perchloride
Red Ferric Oxide	Fe_2O_3 (not less than 90 per cent)	....
Yellow Ferric Oxide	Fe_2O_3 (not less than 97.5 per cent after ignition)	....
Ferric Hydroxide	$Fe(OH)_3$	....
Ferric Sulfate	$Fe_2(SO_4)_3$ (in solution)	....
Ferric Subsulfate	$Fe_4O(SO_4)_5$ (only in solution)	....
Ferric Phosphate	$FePO_4$ (see Soluble Ferric Phosphate N.F.	....
Ferric Hypophosphite	$Fe(PH_2O_2)_3$	....
Ferric Pyrophosphate	$Fe_4(P_2O_7)_3$ (only in solution)	....

Ferric Citrochloride, is obtained in solution.

Iron, Quinine and Strychnine Phosphates N.F. is another bitter tonic. The iron is added in the form of Soluble Ferric Phosphate. According to the N.F., "Soluble Ferric Phosphate is ferric phosphate rendered soluble by the presence of sodium citrate, and yields not less than 12 per cent and not more than 15 per cent of Fe."

The most conspicuous combination of iron in the body is in the hemoglobin of the blood. The average adult has about 2.5 grams of iron in this important combination. Iron is widely distributed through the body; it is present in striated muscle, in the liver, in the spleen, in bone marrow and in blood plasma. Iron is absorbed through the intestinal walls, and excess iron is excreted in the feces. Since copper and manganese are of importance in the diet, these deficiencies are sometimes treated with iron and copper salts (especially for anemia), with iron and manganese salts * or with a mixture of all three salts.

Because ferric ions react with protein to form a precipitate, they are effective as astringents. Ferric Chloride Tincture is commonly used as a styptic and in gargles. Ferric Chloride is also used extensively as a reagent, e.g., in testing for phenolic substances. Ferric ions are precipitated from solution as ferric hydroxide upon the addition of a slight excess of hydroxyl ions according to the reaction

$$Fe^{+++} + 3(OH)^- \rightarrow Fe(OH)_3$$

Solutions containing ferric ions are therefore acid or neutral, e.g., Ferric Chloride Solution N.F.

Metallic iron, because of its physical properties, is very widely used from heavy industry down to very fine and highly spe-

* See Peptonized Iron and Manganese Solution, N.F. VIII, p. 276.

cialized uses. Many types of apparatus are essentially iron. Iron, in special forms, is used medicinally or in the manufacture of iron compounds.

Iron N.F. commonly occurs in the form of a fine, bright wire. When it is bent twice at right angles, so that there are three equal lengths, it is referred to as "card teeth." It also may occur in the form of filings or as a powder. It is used in the preparation of various ferrous salts which may be used as such, e.g., Ferrous Iodide in Ferrous Iodide Syrup N.F.; it is used in the preparation of ferrous salts that may be oxidized to form the ferric salts.

Reduced Iron N.F., a dull, black powder, is obtained by the reducing action of hydrogen when it is passed over heated ferric oxide. It must contain not less than 90 per cent of metallic iron, the remainder consisting of iron oxides. It is commonly used internally, being administered in several pharmaceutical forms. The N.F. describes Reduced Iron Capsules. The usual dose is 500 mg.

Red Ferric Oxide N.F. and *Yellow Ferric Oxide* N.F. are used to produce a flesh color when mixed with Zinc Oxide in making Prepared Neocalamine N.F.

Soluble Ferric Phosphate N.F. is an iron salt which occurs in scale form, although it may also be obtained in the form of granules. It is prepared by adding disodium phosphate to a solution of ferric citrate, and then evaporating the solution at 60° C. to a thick, syrupy liquid. This is then "scaled" on rotating drums or on a glass plate. In this form, it has a bright-green color. The exact composition of this salt is not known; the N.F. requires from 12 to 15 per cent of Fe upon assay. The preparation is soluble in water, but its solution does not contain any ferric ions since the solution does not give any tests for iron. Organic complexes, prepared as scale salts, are also commonly used, e.g., Ferric Ammonium Citrate U.S.P. occurs as garnet-red scales, and Green Ferric Ammonium Citrate N.F. is described as thin, transparent, green scales.

TABLE 58. INORGANIC COBALT COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

COMPOUND	FORMULA
Cobaltous Chloride	$CoCl_2 \cdot 6H_2O$
Cobaltous Sulfide	CoS
Cobaltous Sulfate	$CoSO_4 \cdot 7H_2O$
Cobaltous Nitrate	$Co(NO_3)_2 \cdot 6H_2O$
Cobaltous Carbonate	$CoCO_3$

Cobalt is used, in a limited amount, in certain alloys. Stellite, an alloy containing cobalt and chromium, has been used in the manufacture of surgical instruments and high speed cutting tools. It is also used as a minor component of special steels to give a desired hardness and quality of temper.

The element cobalt probably is properly classified as a "trace" element since only traces of it are required for normal body function. Animal feeding experiments with sheep have shown that a slight amount of cobalt is required; this can be supplied by mixing one pound of cobalt sulfate with 1,600 pounds of salt or by mixing one-half ounce of cobalt carbonate in 100 pounds of salt to which the sheep are allowed free access.[6] It has also been shown that cobalt enhances the effectiveness of penicillin.[7]

The parenteral introduction of the cobalt ion results in a stimulation of the hematopoietic system. A marked increase is observed in the production of erythrocytes and of hemoglobin.

Since cobalt usually is present in sufficient quantity in the normal diet, cobalt compounds are rarely used in therapeutics. Cobalt Chloride (cobaltous chloride) is described in the U.S.P. as a reagent, particularly for use in making Cobaltous Chloride

C.S.[8] for the preparation of "Matching Fluids."[9] These solutions are used particularly in the tests for carbonizable materials in official preparations or compounds.

INORGANIC NICKEL COMPOUNDS OF PHARMACEUTICAL IMPORTANCE. Neither the metal nor any of its compounds are listed in the U.S.P. or the N.F. Nickel is of importance, however, since it is rather widely used in a finely divided form as a catalyst for certain reactions. Hydrogenation reactions are frequently accomplished through the use of this element. Nickel is also used in important alloys and for the plating of other metals. Coinage metal is an alloy of nickel and copper, while German silver is an alloy of nickel, copper and zinc. Monel metal is an alloy of copper and nickel; this metal is used in the manufacture of sinks, table tops, etc.

Capillary damage is observed when nickelous salts are injected parenterally in small amounts. A form of eczema or dermatitis has been observed as the result of somewhat constant contact with the metal.

THE PLATINUM METALS

Platinum was first reported in 1750 by Watson; however, it was probably discovered by Scaliger in the sixteenth century. The name is derived from the Spanish word *platina*, which means silver. Osmium and iridium were discovered by Tennant in 1804; rhodium and palladium were also discovered in the same year by Wollaston. The sixth element, ruthenium, was reported in 1845 by Claus.

Occurrence. These six metals are found associated with each other in nature. They are frequently alloyed together, but have been found, in small amounts, in a few gold deposits. The deposits found in the Ural mountains are the most abundant, but small quantities are obtained from California (U.S.A.), Colombia, Australia, Borneo, South Africa and Canada. They are normally found in the metallic state since their compounds are very easily dissociated to give the free elements.

Physical and Chemical Properties.

TABLE 59. PROPERTIES OF THE PLATINUM METALS

	RUTHENIUM	RHODIUM	PALLADIUM	OSMIUM	IRIDIUM	PLATINUM
Density	8.6	12.1	$11.97^{0° C.}$	22.48	22.4	21.45
Melting point (°C.)	1,950 >	1,966	1,553	2,700	2,440 ± 15	1,773.5
Atomic weight	101.7	102.91	106.7	190.2	193.1	195.23
Atomic number	44	45	46	76	77	78
Atomic volume	8.47	8.9	9.3	8.4	8.6	9.2
Electron distribution	(K) 2-8-18-15-1	(K) 2-8-18-16-1	(K) 2-8-18-18	(K) 2-8-18-32-14-2	(K) 2-8-18-32-17	(K) 2-8-18-32-17-1

Reference to Table 59 shows that the first three elements have atomic weights that are practically the same and that the last three are related to each other in a similar manner. This is to be expected, since the first three elements are transition elements in the second series of 18 elements in the periodic table.

The second group of three elements is composed of transition elements in the series having 32 elements. In addition to atomic weights, the elements are very similar in other properties, both physical and chemical. They all have a silvery luster, are very hard and are resistant to most re-

agents at ordinary temperature. When heated, they are acted upon by fluorine, but the fluorides are decomposed at moderately high temperatures. Palladium is the only element that reacts readily with nitric acid. Aqua regia reacts with all of these elements except rhodium and iridium. Alkaline oxidizing substances, sodium peroxide for example, will dissolve the metals at high temperatures. Alkalies also react with them; this explains the common directions against fusing alkalies in platinum crucibles.

It will be remembered that the iron group of elements is characterized by the valences of two and three. The most characteristic valence of the platinum group is four, but other valences are also exhibited. Ruthenium and osmium form tetroxides, RuO_4 and OsO_4, respectively, thus they apparently have a valence of 8. Osmium also forms the octafluoride, OsF_8. The dioxides are the most stable compounds, and the corresponding hydroxides are slightly basic. The tetrahydroxides are not obtained by hydration of the dioxides, but rather by the action of alkali hydroxides on the tetrachlorides. The monoxides are neither soluble in water nor do they react with water to form the hydroxides. The monoxides exhibit acidic properties, and thus an excess of alkali will tend to combine with the hydroxide as it is formed. Oxides of the type formulae M''_2O_3 and $M''''''O_3$ are also known.

Chlorides having the type formulae $M''Cl_2$ and $M''''Cl_4$ are known for these elements. They have a strong tendency to hydrolyze in aqueous solutions and also form addition products with the alkali chlorides and hydrochloric acid. Thus Palladous Chloride, $PdCl_2$, U.S.P. Reagent, will form a turbid solution in water; the turbidity will clarify upon the addition of hydrochloric acid. Platinic Chloride, U.S.P. Reagent, has the formula $H_2PtCl_6 \cdot 6H_2O$ and is known as "Chloroplatinic Acid." The compound K_2PtCl_4 is called potassium chloroplatinite.

Palladous ions react with Ammonia T.S. to form a salmon-colored precipitate which is redissolved upon the addition of an excess of the reagent. The addition of hydrochloric acid results in the formation of a yellow precipitate of $Pd(NH_3)_2Cl_2$. Potassium Iodide T.S. will produce a black precipitate of PdI_2 when added to solutions of palladous ions.

Platinic chloride is reduced to platinum black upon the addition of zinc. The addition of potassium iodide to a solution of platinic chloride produces a reddish-brown color together with, in some cases, a black precipitate of platinic iodide (PtI_4). This latter compound reacts with an excess of potassium iodide to form potassium iodoplatinate, K_2PtI_6, which is black in color and slightly soluble.

Uses.

Inorganic Palladium Compounds of Pharmaceutical Importance. Neither the metal nor any of its compounds are used for their therapeutic effects. Palladium has the power of occluding hydrogen, one volume of "palladium sponge" being capable of adsorbing approximately seven hundred volumes. The metal is used very effectively as a catalyst for hydrogenation and other reducing reactions. It is also used in gas analysis to adsorb hydrogen. Palladium is used, when alloyed with gold, for making jewelry, dental alloys, etc., since they resist corrosion much better than gold alone. White gold is an alloy; palladium has a greater "whitening effect" than platinum.

Palladous Chloride T.S. U.S.P. may be used for a quantitative estimation of carbon monoxide.

Inorganic Platinum Compounds of Pharmaceutical Importance. Platinum and its compounds are rather widely used but have no known therapeutic value. The metal is used in making jewelry, chemical apparatus such as crucibles and dishes, and also is used as wire and foil. Platinum black, a very finely divided form of the metal, is used as a catalyst, especially for oxidation, e.g., the oxidation of sulfur dioxide to sulfur trioxide in the manufacture of

sulfuric acid. The platinum is normally distributed over surfaces such as asbestos. The metal also occludes hydrogen in a manner similar to palladium.

Platinic chloride, also known as chloroplatinic acid, has the formula $H_2PtCl_6 \cdot 6H_2O$. It is prepared by dissolving platinum in aqua regia then boiling off the nitric oxides in the presence of hydrochloric acid. It occurs as brownish-red, deliquescent crystals which are very soluble in water and are also soluble in ether and alcohol. Platinic Chloride T.S. is made by dissolving 2.6 Gm. in 20 cc. of water and is used as a reagent for the identification of certain alkaloids by the formation of characteristic precipitates. For example, strychnine can be recognized by such a precipitate. This property has also been utilized in molecular weight determinations of unidentified alkaloids.

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The Isotopes of the Elements and Their Uses in Pharmacy, Pharmaceutical Research and Medicine

DISCOVERY AND PRODUCTION
CHARACTERISTICS
RADIOACTIVITY
 UNITS
DETECTION AND MEASUREMENT
APPLICATIONS OF ISOTOPES
 USE AS THERAPEUTIC AGENTS
 USE AS TRACER ELEMENTS
RADIOACTIVE ISOTOPE HAZARDS

The progress of science has been characterized by the invention or discovery of relatively few instruments or technics that have proved to be outstanding in the promotion of science. The analytical balance and the microscope are two examples of instruments that have been of profound significance to such progress. Recently, however, two devices as important as the balance and the microscope have been developed. These devices, the cyclotron and allied instruments and the chain reacting pile, mark the entrance to a new epoch in history, the atomic age and are of profound significance to the pharmaceutical and allied sciences. Their specific application is in the production of isotopes of the elements.

Most of the elements in the periodic table are mixtures of so-called isotopes, and there is at least one isotope and an average of over eight isotopes for every element in the table; over eight hundred isotopes have been discovered and characterized to date. *Isotopes* are defined as elements having the same atomic number but different atomic masses. This means that isotopes have the same number of electrons in the outer shells and the same number of protons in the nucleus but have a different number of neutrons in the nucleus. It is clear, then, that isotopes differ only in the number of neutrons present in the nucleus of the atom and thus the isotopes of any particular element react the same in all chemical and physiologic reactions and cannot be differentiated either chemically or physiologically. Depending upon the stability of the nucleus, isotopes are classified as *stable* or *unstable*. The unstable isotopes are called *radioactive isotopes* since their nuclei disintegrate to a more stable form and in so doing exhibit radioactive properties. It is this radioactive property that makes unstable isotopes so important.

To illustrate the isotopes of an element and their stability, carbon may be taken as an example. There are five known isotopes of carbon; that is to say, there are five different kinds of carbon atoms, all chemically the same since their nuclei carry the same electrical charge. They differ only in their weight; the number of neutrons in the nucleus are responsible for this difference as well as for differences in nuclear stability. The isotopes of carbon weigh ap-

proximately 10, 11, 12, 13 and 14 times as much as the hydrogen nucleus and are designated by the following symbols: $_6C^{10}$, $_6C^{11}$, $_6C^{12}$, $_6C^{13}$ and $_6C^{14}$. Two of these carbons, C^{12} and C^{13}, are stable and occur in nature, while three, C^{10}, C^{11} and C^{14}, are unstable or radioactive and are man-made. Of all the carbon occurring in nature, 99 per cent is C^{12} and 1 per cent is C^{13}, regardless of where the carbon is found. Carbon^{13} existing only in a small percentage of the total is called a *rare stable isotope.*

Radioactive isotopes of the elements have two very outstanding applications: (1) as *sources of radiation* for many potentially important uses and as therapeutic agents when properly used with the necessary precautions and (2) as *tracer elements.* Rare stable isotopes when concentrated over the naturally occurring quantity are also of extreme importance as tracer elements.

DISCOVERY AND PRODUCTION

Discovery and Production of Radioisotopes. Since the earliest days of chemistry, it has been the dream of scientists that some day it might become possible to convert one element into another. No success had been obtained in this artificial disintegration of matter until 1919. Rutherford was the first to see that if a suitable nuclear projectile were available, it might be possible to bring it into such a powerful contact with another nucleus that a proton would be ejected and the bombarded element would be changed into another element in the periodic table. In 1919, Rutherford succeeded in changing a few atoms of nitrogen into oxygen by bombarding nitrogen with alpha particles. In 1934, Curie and Joliot reported that certain light elements which had been bombarded with alpha particles continued to emit radiation for some time after the bombardment was stopped. This marks the discovery of artificial radioactivity. Within a few years, cyclotrons and allied instruments had produced radioisotopes of all of the 83 stable elements. By 1940, some 370 varieties were known, and today over 800 are known. Even though the artificial production of radioisotopes for scientific use dates back only about 15 years, radioactive elements that occur in nature were used as sources of radiation, and even as tracers, in the early years of this century. In 1923, Hevesy reported the first and fundamental experiment with isotopic tracers. He used the naturally occurring radioisotope of lead (radium D) to trace the course of lead in the organism, and his work became the pattern for all future work in this field. Most of the naturally occurring radioactive isotopes belong to the heavy elements between thallium (element 81) and uranium (element 92). None of these is involved in life processes, and therefore, few biologic experiments were performed with the natural radioisotopes; however some of these have been used for treating diseases. Radium and its decay products are the naturally occurring radioisotopes that are used most often.

The use of artificially produced radioisotopes was limited at first since it was tremendously costly to produce isotopes in sufficient quantity in cyclotrons. The development of the atomic energy pile, however, provided a means of producing undreamed of quantities of radioisotopes, and in June 1946, the availability of pile-produced radioisotopes was announced. Since that time, great advances have been made in the production of isotopes, permitting liberal allocations for use in all fields.

Discovery and Production of Rare Stable Isotopes. The history of the discovery and production of rare stable isotopes closely parallels that of radioactive isotopes. Stable isotopes, however, are not manufactured by man as are radioactive isotopes, but are separated from the isotopes with which they occur in the natural elements. After the naturally occurring radioactive isotopes were first observed in 1912, many unsuccessful attempts were

made to separate stable isotopes. However, the development of the mass spectrometer made it possible to observe isotopes, and the important stable isotopes of all elements were identified by 1935. The first success in concentrating a rare stable isotope was achieved in 1930, when "heavy water" (water containing hydrogen enriched in the rare stable isotope H^2) was prepared by distillation. This method, however, was impractical for most elements and was soon superseded by an electromagnetic method of separation developed during the war for separating uranium 235 from its isotopes. As a result of this wartime development, over 100 electromagnetically separated stable isotopes of 29 elements are now available for use. In addition to this, rare stable isotopes of five other elements are produced by physicochemical methods.

CHARACTERISTICS

Radioactive Isotopes. Radioactive isotopes are unstable, and when they disintegrate, energy is released in the form of some type of radiation. There are three types of radiation emitted by natural and artificial radio-elements, namely: *alpha* particles, *beta* particles and *gamma* rays. All of these radiations possess one common physical property—the ability to ionize atoms of the materials through which they pass. It is this ability which is made use of in the detection and characterization of radioactive isotopes.

The *alpha particle* (α) is the nucleus of the helium atom and carries two units of positive charge (protons) and two neutrons. The alpha particle is emitted by many of the natural radio-elements and a few of the artificial radio-elements. Although commonly of high energy, up to several million electron volts, it is characterized by its low penetrating power, never exceeding a few centimeters of air, and by the large number of ions produced per unit of length of path in air.

The *beta particle* is either a high speed electron (β^-) or positron (β^+). A high speed positron has properties identical with those of a high speed electron except that the positron is positively charged. Beta rays made up of electrons are emitted by many natural and artificial radio-elements. Beta rays made up of positrons are emitted by many artificial radio-elements. The beta particle may have energies ranging from a few thousand up to several million electron volts. Like the alpha particle, the beta particle gives up its energy gradually by forming many low energy ions along its path as it proceeds through air, but it forms far fewer ions per centimeter travel and has approximately 200 times the range of an alpha particle of the same energy.

Gamma rays (γ) may be described both in terms of wave and particle properties, and they are emitted from a number of natural and artificial isotopes. Energies of this radiation, traveling with the velocity of light, may vary from a hundred thousand to several million electron volts. Contrary to the alpha and beta particles, the gamma rays are neutral and, therefore, cannot be bent in electric or magnetic fields. On the average, a gamma ray proceeds a considerable distance through a material before it is stopped. Whereas energetic alpha particles are absorbed by a sheet of paper and energetic beta particles by a few millimeters of aluminum, energetic gamma rays may penetrate a sheet of lead a number of inches thick.

Each radioactive isotope is characterized by the type of particle emitted, the energy of the particle emitted and by the characteristic lifetime of the isotope. The life of an isotope is most conveniently designated by the so-called "half-life" period. The *half-life* of a radioactive element is the time required for one-half the atoms initially present to emit their characteristic radiation—the period in which the radioactivity decreases to one-half of its original value. In the next similar period, one-half

the remaining unstable atoms will disintegrate, leaving one-fourth the original activity, etc. This time is constant for any particular radioisotope and ranges from fractions of a second for the most unstable element to billions of years for the most stable.

Rare Stable Isotopes. Rare stable isotopes are characterized by a different mass than the common isotope found in nature. For example, C^{13}, a rare stable isotope, differs only from C^{12}, the common carbon isotope found in nature, by its mass and can be detected only by methods detecting small mass differences.

RADIOACTIVITY

Units. The most commonly used unit for expressing activity is the *curie* (c). A curie is strictly defined as the quantity of radon (0.66 $mm.^3$ at 0° C. and 760 mm.) in radioactive equilibrium with 1 Gm. of radium. The most recent measurements give the value of the curie as $3.67 \pm 0.03 \times 10^{10}$ disintegrating atoms per second. The arbitrary value 3.7×10^{10} disintegrations per second has been selected as the working value and has been applied to expressions of activities of many isotopes. A *millicurie* (mc) is defined as 3.7×10^{7} disintegrations per second and a *microcurie* (μc) is defined as 3.7×10^{4} disintegrations per second. A carefully defined new unit, the "rutherford" has been proposed for general use. The *rutherford* (rd) is defined as the amount of any radioactive isotope which disintegrates at the rate of 10^6 disintegrations per second. This unit is the equivalent of $1/37$ of a millicurie. One *millirutherford* (mrd) is defined as 10^3 disintegrations per second, and one *microrutherford* (μrd) is defined as one disintegration per second.

The "roentgen" (r) is another unit that is used considerably in radioactive work. The *roentgen* is an irradiation unit and is defined as the amount of irradiation which, in 0.0013 Gm. of air, will produce one e.s.u.* of electricity of either sign. The roentgen per hour at one meter (r.h.m.) is also used to measure the radioactivity of beta and gamma emitters.

DETECTION AND MEASUREMENT

Methods of Detection and Measurement of Radioactivity. There are three general methods upon which devices for the detection and measurement of radioactivity are based: (1) measurement of ionization, (2) measurement of fluorescence and (3) effect on a photographic emulsion.

The most used and most sensitive instruments for detecting and measuring radioisotopes depend upon the ionization produced by the emitted particles. Instruments dependent upon this principle include electroscopes, electrometers, cloud chambers and Geiger-Müller counters. The Geiger-Müller counter, a very sensitive instrument, is capable of detecting individually ionized particles and is used more frequently than any other instruments of detection.

When exposed to the radiations from a radioactive source, many substances give off visible light which can be detected readily. The fluorescent screen employed by the radiologist serves as an example of the practical application of this phenomenon. This method has not yet been used extentively for the detection and measurement of radioactivity; however, methods are being developed to measure the amount of activity indirectly by measuring the amount of light striking a photo-electric cell.

Radioactivity may be detected with the "radioautographic" technic, which involves the use of a photographic emulsion. The image produced on a photographic film in contact with a radioactive object is called a *radioautograph*. The term means self-picture by virtue of radioactivity. This technic is of considerable value in the accurate de-

* e.s.u. = electrostatic unit.

termination of the distribution of radioisotopes in various materials.

Methods of Detection and Measurement of Rare Stable Isotopes. Rare stable isotopes are somewhat more difficult to measure and the measurement usually requires much more complicated and expensive apparatus. One of the rare stable isotopes (H^2) may be measured by the simple procedure of measuring differences in the density of the isotopes. This method is possible with H^2 since its mass is twice that of the normal isotope H^1 but is not possible with any other rare stable isotopes since mass differences are considerably smaller, e.g., C^{12} and C^{13}, N^{14} and N^{15}, etc. With all rare stable isotopes except H^2, the mass spectrograph or the mass spectrometer must be used for detection and measurement. This instrument depends upon the separation and focusing of small mass differences in an electric and magnetic field as a means of measurement.

APPLICATIONS OF ISOTOPES

The application of isotopes for peacetime use is divided into three main avenues of endeavor: (1) the pursuit of fundamental atomic research, most likely leading to further constructive applications and certainly to advances in human knowledge; (2) the development of useful power, leading to possible economic and sociological gains; (3) the use of radioactive products, leading to knowledge and beneficial applications in a wide range of scientific, industrial and medical fields.

There are two very outstanding uses of radioactive products in pharmacy, pharmaceutical research and medicine at the present time; they are used (1) as therapeutic agents when used properly and with necessary precautions and (2) as tracer elements.

Use as Therapeutic Agents. As therapeutic agents, radioactive isotopes by virtue of their radiations are drugs, in the true sense of the word, and are so classified and regulated under Section 505 of the U. S. Federal Food, Drug, and Cosmetic Act. The rays emitted when a radioactive isotope disintegrates are a source of penetrating radiation in the treatment of abnormal tissues; the injury to unwanted tissue must be notably greater than the injury to normal, essential tissue.

Radium and radon, naturally occurring radioisotopes, have been used for years in the treatment of various conditions because the ionizing radiation emitted from these isotopes destroys tissue. Three artificially produced radioisotopes are employed in the form of their salts in therapy with some success. These are radioactive phosphorus-32, radioactive iodine-131 and radioactive iodine-130. Certain other isotopes, for example, sodium-24, gold-198 and cobalt-60, are undergoing therapeutic evaluation.

Phosphorus-32 was the first artificially produced isotope to be used in medicine. It is usually administered orally or intravenously in isotonic soluble form as Na_2HPO_4. The general view taken by physicians at the present time is that phosphorus-32 therapy is the treatment of choice for many cases of polycythemia vera, a single course of treatment in most cases bringing about a remission of the disease and symptomatic relief lasting from several months to several years. In addition, phosphorus-32 therapy is at least as satisfactory as x-ray treatment in producing remission and symptomatic relief in the treatment of both lymphatic and myelogenous chronic leukemia and has the added advantage that radiation sickness is rarely produced. Phosphorus-32 labeled phosphate solution also has been used with success in the treatment of certain susceptible skin lesions.

The therapeutic use of radioactive iodine has been reported for the treatment of hyperthyroidism of various types and for the treatment of iodine-metabolizing thyroid malignancies. For these purposes, carrier-free radioiodine in the form of an aqueous sodium iodide solution is administered by

mouth. The radioiodine used usually consists of a mixture of iodine-130 and iodine-131, of which the former is clinically the more important part of the mixture. For the diagnosis and treatment of certain thyroid diseases, radioactive iodine therapy shows great promise.

In addition to the direct use of radioactive isotopes in therapy, there are several indirect uses as therapeutic aides. Among these are: (1) use in the production of modified forms of materials commonly prepared by manufacturing pharmacists, (2) use in the study and treatment of radiation damage and (3) use as diagnostic agents. Radioactive isotopes have not been used as yet in the production of modified forms of pharmaceuticals; however, the possibilities of using the effects of radiation in the production of modified strains of bacteria, viruses, fungi and actinomycetes, in the denaturation of proteins and in the inactivation of enzymes are apparent, and may have considerable application. The use of radioactive isotopes in the study and treatment of radiation damage is new; however, various drugs and various types of treatment are being tested in an effort to decrease the extent of radiation damage and sickness. Such uses of radioactive isotopes are important in cases of possible human overexposure in radiation therapy, atomic energy work and warfare.

Radioactive isotopes have now become of value as diagnostic agents, for example, in checking blood volume and blood circulation. This is done by injecting normal saline containing radioactive sodium into the veins of the patient. The volume, efficiency rate and extent of blood circulation then can be measured easily. This has proved to be an extremely valuable tool when amputation, particularly of a gangrenous limb, must be attempted. Radioactive iodine is also being used as an aid in diagnosing various types of thyroid disorders.

The use of radioactive isotopes as therapeutic agents is a recent development, and advances in their use for these purposes may be expected.

Use as Tracer Elements. The most important use of isotopes is as tracer elements. Both radioactive and rare stable isotopes may be used as tracer elements. In the future, these tracer isotopes may well become routine laboratory tools, and the results obtained with them will no more be put into a separate category and discussed in special papers than are the results obtained using analytical balances and microscopes today. The services that isotopes are capable of performing are applicable to all branches of science, medicine, agriculture and industry and are so fundamental that no complete inventory will ever be made of their potential uses. Since pharmacy, pharmaceutical research and medicine are chiefly the application of all branches of science to the production and usage of medicinals and medicinal products, isotopes have particular application in the various divisions of these professions.

The basis for the use of isotopes as tracer elements depends on the fact that ordinary physical and chemical processes cannot be used to distinguish between the various isotopes of an element. Since an isotope of an element behaves the same as other isotopes of the element in all chemical and physiologic processes, it labels without question the particular atoms one wishes to trace, regardless of their incorporation into units with other atoms or into any combination in which one might desire to trace them. In other words, isotopes afford the ultimate in specificity for the tagging of an atom or element.

The advantages of the use of radioactive isotopes as tracer substances may be listed as follows. (1) The movement of tagged substances is easily followed using suitable detection devices. (2) Small amounts of the tagged substance may be used. As an example, as little as 10^{-7} Gm. of iodine, 0.1 microgram, is sufficient for the tracer technic using radioactive iodine. (3) It is often un-

necessary to remove organs or tissues or to kill the organism in order to determine the presence and content of radioactive material. (4) The detection of elements by their radioactivity is up to one million times as sensitive as it is by the usual methods of chemical or physical analysis. This means that roughly 10^{-18} Gm. to 10^{-20} Gm. of the substance often can be detected readily. Such sensitivity of measurement makes possible the intelligent study of problems which heretofore could not be solved by the use of existing methods or tools.

In general, the tracer procedure involves the preparation of a labeled compound (tagging), the introduction of this compound into the system to be studied and then the determination of the concentration and distribution of the compound by the available means of detection and measurement. Thus, the pathway of the material can be determined by following the easily detectable isotope through a series of complex changes. Not only can the pathway of the material be followed, but also the quantities of material involved can be determined. By such means, reaction mechanisms, analytical problems, manufacturing problems, metabolic problems, etc., can be studied and solved.

There have been many important findings as a result of the use of tracer isotopes and no attempt is made to list them. However, a single specific example will indicate the type of information which can be obtained. Radioactive iron has been used as a tracer to unravel the biochemical role of iron as well as the physiologic aspects of iron absorption and excretion. It has been found that absorption of iron from the intestines is regulated by the amount of iron reserve. If the reserve is high, little or no iron is absorbed; and the iron present in the body is continually used over and over instead of being eliminated and replaced. When hemoglobin, labeled by the incorporation of labeled iron, is liberated by erythrocyte destruction, the labeled iron of the hemoglobin is promptly reutilized to form new hemoglobin. Thus, through the use of a tracer, it is shown that the animal body is very efficient in utilizing its iron and that under normal conditions elimination of iron from the iron cycle is maintained at a low level.

Although the number of radioactive isotopes available at the present time is very great, not all of them have properties which permit their use as tracer elements, particularly in biologic work. The desirable properties for radioactive tracer isotopes may be summarized as follows. (1) The half-life of the isotope must be sufficiently long so that decay does not remove the tracer faster than it can be extracted, characterized and assayed. On the other hand, the half-life should not be longer than necessary. The disadvantage of using an isotope with a long half-life is that laboratories and laboratory animals are not self-cleaning. With an isotope like phosphorus-32 (half-life 14.8 days), animals which have been used for experimental purposes may be used again some months later when all radioactivity has decayed away. The same will be true with laboratory equipment, etc. Using an isotope like C^{14} (half-life 5,100 years), it is necessary to observe the utmost precautions in preventing contamination of floors, equipment, etc., since contaminated areas remain active with an isotope for a minimum time of ten half-life periods or in the case of carbon, 51,000 years. (2) Special precautions must be taken with isotopes which emit alpha particles since these affect normal tissues to the greatest extent when in contact with the tissue. (3) The radiations emitted must be of sufficient energy to permit detection. (4) The initial concentration of the tracer to be used must be sufficient to withstand dilution during the process through which it is to be traced, but it must not be so great that the radiation emitted will interfere with the system being studied or cause damage of tissue. In biologic investigations

it is advisable to keep the concentration of labeled molecules low in relation to the concentration of the same molecules already present in the unlabeled state. (5) The tracer isotope must adhere to the particular molecule or portion of molecule with which it is originally incorporated. Thus, processes involving the removal of the tracer by direct "exchange" reactions must be minimized or obviated by control experiments.

The important available radioactive isotopes with desirable characteristics for biologic tracer experiments are listed in Table 60. Table 61 lists the labeled compounds available for study.

Probably the most important radioactive isotopes from the standpoint of future possibilities are Carbon-14 (C^{14}) and Hydrogen-3 (H^3). Although they are not ideal tracers because of the low energy of radiation and the long half-life, these disadvantages are counterbalanced by their great importance. Since they are the radioactive isotopes of the building-stones of all organic materials, they have become tools which scientists in pharmacy, medicine, biology and organic chemistry have dreamt of for years.

It has been mentioned previously that rare stable isotopes may also be used as tracer elements. They have not been used as widely as radioactive isotopes since they have not been made as readily available and have certain disadvantages, the most important of which is the need of a mass spectrograph for detection and measurement. As yet, there are not many of these instruments available for use.

More than 100 varieties of rare stable isotopes of 29 elements have been separated. Only five of these isotopes are available in relatively liberal supply; however, these five are the more important ones. They are: (1) hydrogen-2 (deuterium), (2) boron-10, (3) oxygen-18, (4) carbon-13 and (5) nitrogen-15. Of these five, oxygen-18 and nitrogen-15 are of particular importance to biologic work since they are present in a great majority of biologically important substances and since there are no suitable radioactive isotopes of these two elements. All the rest of the elements in the periodic table have at least one usable radioactive isotope.

Applications of Isotopes as Tracer Elements. It is not possible to list all the applications of isotopes as tracer elements; however, it is informative to list a few of the uses as examples of the significance of the method. Applications in the medical and allied fields have accounted for 40 per cent of the total use of isotopes since they have become available.

Examples of tracer isotope applications are as follows.

A. *Pharmacology:*

1. Determination of skin residues;
2. Determination of calcium-phosphorus depletion of teeth and bones;
3. Determination of the rate of absorption, excretion, alteration, breakdown and per cent distribution in various organs of many synthetic organic medicinal substances and natural medicinal substances which can be biologically synthesized in the presence of radioactive carbon dioxide;
4. Determination of isotope distribution in individual cells, the radioautographic technic is employed;
5. Tracing a variety of bodily ingredients, such as alcohols, amino acids, antigens, bacteria, bile acids, blood cells, carbohydrates, carcinogens, enzymes, fats, fatty acids, hormones, insulin, nucleic acids, penicillin, proteins, starches, viruses, vitamins, etc.;
6. Studies to learn more about the functioning of every important organ.

B. *Pharmaceutical Chemistry:*

1. Determination of the solubilities of very slightly soluble compounds in the pure state or in the presence of foreign ions;
2. Determination of the amount of a given substance that is absorbed or occluded during a precipitation or purification procedure;

TABLE 60. IMPORTANT RADIOACTIVE ISOTOPES AVAILABLE FOR BIOLOGIC EXPERIMENTS *

Isotope	Half-life	Energy Max. (M.E.V.)		Compound	Total Activity (Millicuries)	Total Cost of Total Activity Listed
		Beta	Gamma			
Available from the Pile						
C-14 (H.S.A.)	5,100 yr.	0.154	...	CH_3OH	1	$100.00
				$BaCO_3$ (4 per cent C-14)	1	36.00
I-131 (H.S.A.)	8.0 da.	0.6	0.367, 0.080	NaI	1	1.00
P-32 (H.S.A.)	14.3 da.	1.69	...	Na_2HPO_4	1	1.10
P-32 +	14.3 da.	1.69	1.51	KH_2PO_4	350	33.00
K-42	12.4 hr.	3.58, 2.07	1.51		140	
S-35 (H.S.A.)	87.1 da.	0.17	...	H_2SO_4	1	2.40
				Na_2S	1	6.00
Ca-45 (H.S.A.)	180 da.	0.3	...	$CaCO_3$	1	2.20
As-76	26.8 hr.	1.1, 1.7, 2.7	0.57, 1.25	As_2O_3	25	12.00
Cs-134	2 yr.	0.645	0.584, 1.35	Cs_2CO_3	20	34.00
Cr-51	26.5 da.	K	0.32	Cr	50	34.00
Co-60	5.3 yr.	0.3	1.1, 1.3	Co_3O_4	20	33.00
Cu-64	12.8 hr.	0.66, 0.58, K	1.2	Cu	100	12.00
Ga-72	14.1 hr.	3.1, 0.8	0.84, 2.25	$Ga(NO_3)_2$	25	21.00
Au-198	2.7 da.	0.97	0.44	Au	80	12.00
Hf-181	46 da.	0.8	0.5	Hf_2O_3	50	31.00
Ir-192 +	75 da.	0.59	0.2, 0.6	IrO_2	40	35.00
Ir-194	19 hr.	2.07	0.38, 1.65		200	
La-140	40 hr.	0.9, 1.40, 2.12	1.63	La_2O_3	40	12.00
Ni-59	15 yr.	K, e^-	...	Ni	1	33.00
K-42	12.4 hr.	3.58, 2.07	1.51	K_2CO_3	130	12.00
Pr-142	19.3 hr.	2.14	1.9	Pr_2O_3	40	13.00

* H.S.A. = high specific activity, M.E.V. = million electron volts, K = K-capture process of decay, e^- = negative beta ray.

TABLE 60. IMPORTANT RADIOACTIVE ISOTOPES AVAILABLE FOR BIOLOGIC EXPERIMENTS * (*Continued*)

Isotope	Half-life	Energy Max. (M.E.V.) Beta	Energy Max. (M.E.V.) Gamma	Compound	Total Activity (Millicuries)	Total Cost of Total Activity Listed
Available from the Pile						
Rb-86	19.5 da.	1.60	....	Rb_2CO_3	100	$62.00
Se-75	125 da.	K, e^-	0.3	Se	65	33.00
Ag-110	225 da.	0.59	0.66, 0.90, 1.4	$AgNO_3$	35	33.00
Na-24	14.8 hr.	1.4	1.4, 2.8	Na_2CO_3	20	12.00
Sr-89	55 da.	1.5	....	$Sr(NO_3)_2$	1.5	33.00
Ta-182	117 da.	0.53, 1.13	1.22	TaO_2	40	33.00
Tl-204	2.7 yr.	0.58	....	$Tl(NO_3)_3$	7	33.00
Y-90	62 hr.	2.16	....	Y_2O_3	100	33.00
Zn-65 +	250 da.	0.4, K	1.14	Zn	15	33.00
Zn-69	13.8 hr.	1.0	0.49		60	
Zr-95	65 da.	1.0, 0.394	0.73, 0.92	$Zr(OH)_4$	12	12.00
H-3	31 yr.	0.015	....	H_2 Gas	1	0.20
Available from the Cyclotron †						
Be-7	43 da.	K	0.485			
F-18	118 min.	0.7	....			
V-47	600 da.	K	....			
Mn-52	6.5 da.	0.77	1.0			
Mn-54	310 da.	....	0.845			
Ni-57	36 hr.	0.67	....			
Xe-127	34 da.	....	0.9			
Pb-203	52 hr.	....	0.27			
Na-22	3 yr.	0.58	....			

† Availability, quantity and prices obtainable only on request to various organizations operating cyclotrons or allied instruments.

TABLE 60. IMPORTANT RADIOACTIVE ISOTOPES AVAILABLE FOR BIOLOGIC EXPERIMENTS* (*Continued*)

Isotope	Half-life	Energy Max. (M.E.V.)		Compound	Total Activity (Millicuries)	Total Cost of Total Activity Listed
		Beta	Gamma			
Available from the Cyclotron †						
Fe-59	44 da.	0.26, 0.46	1.3			
Fe-55	4 yr.	K	0.08			
As-74	16 da.	1.3, 0.9	0.582			
As-73	90 da.	K	0.052			
I-130	12.6 hr.	0.61, 1.03	0.42, 0.54			
C-11	21 min.	0.95	....			

3. Study of colloids and their properties;
4. The isolation, purification and identification of substances existing in small quantities in complex mixtures;
5. Synthesis of tagged molecules;
6. Study of the processes involved in molecular formations and exchanges, in the diffusion of liquids and solids, in the interactions among gases, liquids and solids, in catalytic action, in complex chemical and biochemical reactions, etc.

C. *Pharmacognosy:*
1. The production of natural plant extracts;
2. The production of antibiotics;
3. Under natural conditions and in conjunction with hydroponics, the study of the rate of uptake, distribution and elimination of various elements, radicals and compounds in plants;
4. The study of the uptake, utilization, storage, elimination and requirements in plants of certain trace elements, such as Cu, Co, Ni, Cr, etc.

D. *Pure Pharmacy:*
1. The determination of the rate of uptake, utilization and elimination of medicaments administered in various types of pharmaceutical preparations;
2. The determination of disintegration rates of tablets and enteric-coated medicaments in vivo;
3. The determination of uniform distribution of drugs in various medicament forms;
4. To follow and measure a variety of medicinally important substances otherwise untraceable in order to establish better and more economical drug production.

E. *Industrial Research and Metallurgy:*
1. In the manufacture of steel, machinery, rubber, gasoline, oil, plastics, rayon, chemicals and many other products to bring better and more economical production;
2. To study the structure, manufacture, alloying, durability, corrosion and friction of metals;
3. To study the precise distribution of

TABLE 61. LABELED COMPOUNDS AVAILABLE *

COMPOUND	ISOTOPE	COST/MC
AVAILABLE FROM TRACERLAB, BOSTON 10, MASSACHUSETTS		
Barium Carbide	C-14	$150.00
Acetylene	C-14	350.00
Sodium Cyanide	C-14	250.00
Methanol	C-14	250.00
Methyl Iodide	C-14	285.00
Sodium Acetate	C-14 (Carboxyl carbon)	225.00
Ethyl Acetate	C-14 (Carboxyl carbon)	275.00
Ethanol	C-14 (Methylene carbon)	300.00
Ethyl Iodide	C-14 (Methylene carbon)	350.00
Toluene	C-14 (Ring carbon)	500.00
Benzoic Acid	C-14 (Ring carbon)	550.00
Benzene	C-14	600.00
AVAILABLE FROM THE TEXAS RESEARCH FOUNDATION, RENNER, TEXAS		
Methionine	S-35	500.00
Cystine	S-35	500.00
Cysteine	S-35	500.00
Glutamic Acid	C-14 (Carboxyl)	500.00
Tyrosine	C-14 (Beta carbon on side chain)	500.00
Diiodotrypan Blue	I-131	250.00
Evan's Blue	I-131	†
Stearic Acid	C-14 (Carboxyl carbon)	†
Deuterated Ammonia	H-2 (Stable) ND_3	†
Deuterated Acetylene	H-2 (Stable) $DC\equiv CD$	†
AVAILABLE FROM ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS		
Colloidal Gold	Au-198 (Solution 5-8 mc/cc.)	†
Gold Sodium Thiosulfate	Au-198 (1-1.6 mc/mgm.)	†
Thiourea	S-35	†
Pentothal	S-35 (1 μc/mgm.)	†
Diiodo Fluorescein	I-131 (3 per cent solution 10 mc/gm.)	†

* Compounds available as of January 1, 1949. The number of labeled compounds available is being increased rapidly.

† Prices quoted on request.

isotope-tagged material in metals and other substances by the radioautographic technic;

4. Surveying to determine the location and quantities of oil and water underground;

5. Testing petroleum products in operating engines;

6. In studying the vulcanization and polymerization processes;

7. To dissipate hazardous and hampering

static electricity which collects on belts, rolls of paper and other moving materials in factories;

8. In measuring the thickness of materials accurately to a hundred thousandth of an inch;

9. In the production of control instruments.

These applications are but a few of the total possible uses of isotopes as tracer elements, but they are of sufficient number and variety to show that isotopes are research and industrial tools capable of many-sided applications.

RADIOACTIVE ISOTOPE HAZARDS

A discussion of isotopes and their applications cannot be considered complete without information concerning the health hazards and contamination hazards of tracer amounts (the millicurie level) of radioactive isotopes. Rare stable isotopes do not present hazard problems as do radioactive isotopes.

There are two main considerations in the use of radioactive isotopes at the millicurie level. These are: (1) contamination of the working area and (2) radiation health hazards. Contamination problems are, in general, a function of the half-life of the isotope which is involved, while radiation health hazards are dependent upon the amount and energy of the activity present. For example, both sodium-24 (14.8 hr. half-life, 1.4 M.E.V. beta and 2.8 M.E.V. gamma) and potassium-42 (12.4 hr. half-life, 75 per cent 3.58 M.E.V. beta, 25 per cent 2.07 M.E.V. beta and 1.51 M.E.V. gamma) present substantial health hazards in millicurie amounts since they emit high energy beta and gamma radiations, but they present only minor contamination hazards since they have short half-lives. On the other hand, when working with high millicurie strengths of a pure beta emitter with a long half-life (for example, Ca^{45}, 180 day half-life, 0.3 M.E.V. beta), the health hazard of external radiation is small (internal radiation is dangerous) while the contamination hazard is considerable. When using weak beta emitters of long half-life (for example, C^{14}, 5,100 year half-life, 0.15 M.E.V. beta and S^{35}, 88 day half-life, 0.15 M.E.V. beta) one need not be concerned about external radiation even with considerable amounts since the beta ray emitted will not penetrate matter for a distance great enough to cause difficulty. On the other hand, the internal deposition of relatively small amounts (10 to 20 microcurie or greater) of these substances may be quite dangerous. This is true especially of C^{14} since a substantial portion is fixed in the bone, where it may remain for many years irradiating the bone structure and possibly giving rise to abnormal conditions. These two isotopes also present a contamination problem because of their long half-lives.

Under health hazards, there are two considerations, depending on the isotope, (1) external radiation and (2) internal radiation. It is evident that the relative importance of these factors is to a great extent dependent upon the radioisotope being handled. However, by far the most important consideration is the prevention of the absorption into the body of long-lived radioisotopes. Such absorption may occur through the alimentary tract, through the lungs (especially important with gaseous materials such as radioactive CO_2, SO_2 and SO_3) and through wounds or injection. In certain instances, amounts sufficient to cause concern may be absorbed through the normal skin.

In no instance should radioisotopes be processed in a room used for radioassay work. The reason for this rule is obvious when one considers the orders of magnitude of the activities involved. The amount necessary for counting is in the order of 10^{-4} microcuries or less. It is sometimes necessary to handle or process as much as a billion times this amount of activity. In view

of this, it is usually impossible to prevent contamination unless three physically isolated rooms are provided for stages in the radioactive work: namely, (1) the microcurie level where radioassay work is done, (2) the intermediate level where experimentation takes place and (3) the millicurie level where isotopes are stored or processed.

Although it is apparent that many precautions must be taken, radioisotope work is fundamentally no more hazardous than work involving poisonous materials or high voltage. It is true, however, and this point should be emphasized, that only those responsible individuals who are willing to abide by certain precautions and safety measures should undertake to handle radioactive isotopes. Some workers worry over the possibility of excessive exposure, while others set aside all fear of radiation and become careless. In either case, accident probability is greatly increased. The most desirable attitude is one not of fear, but of taking adequate precautions for protection, after which there is no need for fear.

New as they are, the uses of radioactive isotopes in the medical fields and the uses of isotopes, radioactive and stable, for tracer applications have already broadened our understanding of many fundamental processes of nature. Already, medical men are profiting from a better understanding of the working of the human body. More lives have already been saved through the use of isotopes than were lost at Hiroshima and Nagasaki. For the future, it is difficult to forecast the gains that isotopes will bring. They will speed the battle against disease; they will help man to make more efficient use of nature's materials, to grow more food, to produce better manufactured goods—in short, to adapt his environment to his needs.

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